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Systematic Review of Studies That Have Evaluated Screening Tests in Relatives of Patients Affected by Nonsyndromic Thoracic Aortic Disease

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***Background*—**Nonsyndromic thoracic aortic diseases (NS-TADs) are often silent entities until they present as life-threatening emergencies. Despite familial inheritance being common, screening is not the current standard of care in NS-TADs. We sought to determine the incidence of aortic diseases, the predictive accuracy of available screening tests, and the effectiveness of screening programs in relatives of patients affected by NS-TADs.

***Methods and Results*—**A systematic literature search on PubMed/MEDLINE, Embase, and the Cochrane Library was conducted from inception to the end of December 2017. The search was supplemented with the Online Mendelian Inheritance in Man database. A total of 53 studies were included, and a total of 2696 NS-TAD relatives were screened. Screening was genetic in 49% of studies, followed by imaging techniques in 11% and a combination of the 2 in 40%. Newly affected individuals were identified in 33%, 24%, and 15% of first-, second-, and third-degree relatives, respectively. Familial NS-TADs were primarily attributed to single-gene mutations, expressed in an autosomal dominant pattern with incomplete penetrance. Specific gene mutations were observed in 25% of the screened families. Disease subtype and genetic mutations stratified patients with respect to age of presentation, aneurysmal location, and aortic diameter before dissection. Relatives of patients with sporadic NS-TADs were also found to be affected. No studies evaluated the predictive accuracy of imaging or genetic screening tests, or the clinical or cost-effectiveness of an NS-TAD screening program.

***Conclusions*—**First- and second-degree relatives of patients affected by both familial and sporadic NS-TADs may benefit from personalized screening programs. **(*J Am Heart Assoc*. 2018;7:e009302. DOI: 10.1161/JAHA.118.009302.)**

Key Words: aortic disease • genetic testing • mortality • screening

Diseases of the thoracic aorta are increasing in prevalence, accounting for 1% to 2% of all deaths in Western countries.[1–5] In the United States, diseases of the aorta account for more than 40 000 deaths per year.[1,4] Thoracic aortic diseases (TADs) are often silent entities with a mortality of almost 80% when presenting as life-threatening emergencies.[3,6] Therefore, early diagnosis and treatment are likely to improve long-term survival. TADs may be syndromic, associated with disorders involving other organs such as Marfan syndrome, or more commonly nonsyndromic, with manifestations restricted to the thoracic aorta.[4,5] Nonsyndromic TADs (NS-TADs) may be familial, characterized by the presence of a family history and an autosomal dominant inheritance, or sporadic.[4–7] Unlike syndromic TADs, NS-TADs are not evident from external physical features and abnormalities of other organ systems and are characterized by silent aneurysm formation and dissection.[4,5] Screening of first-degree relatives (FDRs) of patients affected by NS-TAD is therefore recommended for early detection and treatment of asymptomatic disease.[4,5] However, existing guidelines are based predominantly on the consensus of expert opinion, rather than high-quality evidence, and the testing modality, frequency, and extent (FDRs versus second-degree relatives [SDRs]) of screening are not defined.[4,5] As a consequence, there is widespread variation in the screening of family members of patients with NS-TADs. To address this area of

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Accompanying Data S1, Tables S1 through S11, and Figures S1 and S2 are available at http://jaha.ahajournals.org/content/7/15/e009302/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- Imaging and/or genetic screening is not the current standard of care in relatives of patients affected by nonsyndromic thoracic aortic diseases (NS-TADs).
- Genetic and/or imaging screening of relatives of patients affected by NS-TAD can detect more than 30% of patients newly affected by thoracic aortic diseases.

What Are the Clinical Implications?

- Routine imaging and genetic testing of relatives of patients affected by nonsyndromic aortopathies should be encouraged.
- The evidence suggests that screening of first- and second-degree relatives of patients affected by familial NS-TAD and first-degree relatives of those affected by sporadic NS-TADs will result in significant numbers of patients with otherwise undiagnosed disease.
- Personalized screening programs determined by the subtype of NS-TAD and its related genetic mutation have the potential to benefit these patients.

uncertainty, we performed a systematic review of the evidence for screening in the relatives of patients affected with NS-TADs with reference to the prevalence of aortic disease, the predictive accuracy of genetic and imaging screening tests, and the effectiveness of screening programs in this high-risk population.

Methods

The data, analytic methods, and study materials are available to other researchers for purposes of reproducing the results or replicating the procedure (Supplemental Material).

Protocol, Registration, and Search Strategy

The search strategy, objectives, study selection and eligibility, data collection, and assessment of study quality are published online and registered in the PROSPERO International Prospective Register of Systematic Reviews (PROSPERO registry—CRD42017064598).[8] The protocol of the present systematic review is fully reported in Data S1. The review adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Table S1).[9]

We searched electronic databases (PubMed/MEDLINE, Embase, and Cochrane Library) without date or language restriction from inception to the end of December 2017. A systematic search in the Online Mendelian Inheritance in Man (OMIM) database[10] on December 31, 2017, was also accomplished. To supplement the electronic search, the "first-generation" reference lists of pertinent articles were reviewed. Search criteria, adopted keywords, and MeSH terms used in relevant combinations are reported in Data S1.

Participants

We included studies considering imaging and/or genetic screening tests in probands affected by diseases of the thoracic aorta (aneurysms and/or acute aortic syndrome), and their FDRs, SDRs, and third-degree relatives (TDRs), with no restriction on ethnicity or age.

Target Condition

The target condition was disease of the thoracic aorta (aneurysm and/or acute aortic syndrome) defined by the international guidelines on diagnosis and management of patients with TAD.[4,5] Only NS-TAD forms were considered in the present review; syndromic TADs or other *forme fruste* of syndromic TAD related to the transforming growth factor β pathway were excluded. Familial NS-TAD forms were defined as those occurring in families with ≥2 members with a known TAD, but without a clinical diagnosis or history of a syndromic TAD or any other connective tissue disease.[7] Sporadic TADs were defined as those occurring in patients apparently without a family history of TAD or evidence of syndromic TAD.[4,5,7]

Index Tests

For the purposes of the review, we included studies that phenotyped participants using the following imaging tests: transthoracic echocardiogram (TTE)/transoesophageal echocardiogram, computed tomography (CT), or magnetic resonance imaging (MRI) of the thoracic aorta, and genetic screening, individually or in combination with the acknowledgement that sensitivities and specificities of CT (100% and 100%, respectively) and MRI (95–100%) are higher when compared with those of transoesophageal echocardiogram and TTE (74–100% and 71–91%, respectively).[11–15] In some studies, surgery for TAD, postmortem examination, or sudden death were used to assess the aortic phenotype. Molecular genetic testing approaches included a combination of gene-targeted testing (multigene panel or single gene testing) and whole exome of genome sequencing.[16–18]

Study Selection, Data Collection, and Extraction

Two investigators (G.M. and R.D.) independently reviewed titles, abstracts, and full-text articles against the specified inclusion criteria for studies regarding screening of relatives

of patients with NS-TADs. Discrepancies were resolved through consensus and consultation with a third investigator (G.J.M.). One reviewer extracted key data from the included studies using a standard dedicated pro forma; a second reviewer checked the collected data for completeness and accuracy. The Tables report full details on study design and quality, setting and population, details, and results of screening. Key study characteristics include details of the patient population (NS-TAD form, ethnicity, family identification), participants undergoing screening (relatives eligible for screening; family pedigree; total number of screened relatives; numbers of FDRs, SDRs, and TDRs), TAD characteristics (new diagnosis of aortic disease, number/rate of newly diagnosed thoracic aortic aneurysms and/or dissection, rate of unexplained sudden death, age and aortic diameters at dissection, sex preponderance, and aortic disease penetrance), additional concomitant phenotype/clinical features (types and rates), and type of adopted screening modality (imaging and genetic test used, validation processes). The definitions of the extracted variables are fully reported in Data S1.

Quality Assessment, Data Synthesis, and Analysis

Two investigators (G.M., R.D.) independently appraised all articles that met inclusion criteria. Study quality was assessed using the Newcastle-Ottawa Scale and the US Preventive Services Task Force.[19,20] The Cochrane Risk of Bias tool was also used to evaluate the methodological quality of all included studies.[21]

Because of the observational nature of the studies and their clinical heterogeneity, the analyses were largely descriptive, and a narrative and tabular synthesis of all included studies is provided. Inclusion and exclusion criteria for qualitative/quantitative analyses are summarized according to the PICOS (population, intervention, comparator, outcomes, and study design) approach (Table S2). Subgroup analysis considering type of NS-TAD form, aortic disease (aneurysm and/or dissection), genetic mutation, and screening modality was also conducted. Categorical variables are reported as number and percentage, and continuous variables are reported as mean and SD or median and range, according to distribution. Analyses were performed with SPSS version 24.0 (IBM).

Results

Description of Studies and Quality Assessment

Of the 12 897 records identified, 53 studies were included in the systematic review, comprising a total of 2696 screened relatives. The studies were published between 1985 and 2017 (Figure S1).[22–74] Regions of origin included North America (28 studies), Europe (17 studies), Asia (5 studies), and Australia (3 studies) (Table 1). No randomized trials were identified, and only 1 large cross-sectional study was conducted including 581 at-risk relatives.[58] Study characteristics and collected outcomes are summarized in Tables S3 through S8 and study quality assessment in Table S9.

Target Condition

Four main groups of familial NS-TADs were identified: (1) those characterized by the presence of both aneurysms and dissections in the family pedigree (familial thoracic aortic aneurysm and dissection; 44 studies); (2) those characterized by aneurysmal disease only (familial thoracic aortic aneurysm; 2 studies); (3) those characterized by aortic dissection only (familial thoracic aortic dissection; 3 studies); and (4) thoracic aortic aneurysm forms associated with the presence of bicuspid aortic valve (4 studies). Among the familial thoracic aortic aneurysm and dissection forms, 3 additional subgroups were discovered based on the concomitant presence of patent ductus arteriosus (n=4), intracranial aneurysms (n=2), or peripheral arterial aneurysms (n=2) (Table 1).

Index Tests

Screening for TAD was performed using 2-dimensional TTE in 27 (51%) studies, of which 15 (28%) employed 2-dimensional TTE alone and the remaining 8 (15%) used 2-dimensional TTE in association with CT and/or MRI. In 5 (9%) studies only, imaging screening included the simultaneous employment of 2-dimensional TTE, CT, and MRI. In a further 26 (49%) studies, aortic phenotype (presence of an aortic aneurysm and/or dissection) was defined by reported clinical events including acute aortic syndrome, diagnosis made during routine diagnostic clinical care, or postmortem examination. The aortic diameter cutoff used for defining a critical dilation of the aorta varied among studies as the aortic site where the measurements were made (Table S7).

No study reported the sensitivity, specificity, or other measures of diagnostic accuracy for the index tests. One study reported 10-year longitudinal follow-up for relatives of patients with NS-TAD.[59] In this study, relatives with evidence of aortic dilatation were offered annual follow-up imaging with prescription of β-blockers or angiotensin receptor blockers at maximal tolerated doses. Relatives with no evidence of aortic dilatation (unaffected) were subjected to clinical review every 3 years. In the affected relatives (n=114) with serial aortic measurements over 4.5±4.4 years, a mean rate of increase in the aortic diameter of 0.56±0.76 mm per year was observed. No difference in the rate of aortic dilatation was observed between males and females or in patients receiving

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Table 1. Details of Studies Included in the Systematic Review

Study (Author/Y)	Country	NS-TAD Form	Pedigree (Patients)					Relatives Affected		Penetrance, %	Inheritance (Modality)	Type of Screening	Related Gene
			Total, No.	FDRs, No.	SDRs, No.	TDRs, No.	Probands, No.	No.	%				
Barbier et al 2014[22]	France	FTAAD	40	14	14	0	2	7	18	60	AD	GEN+IMAG	MFAP5
Bee et al 2012[23]	United States	FTAA	54	37	3	0	9	12	22	100	…	GEN	ACTA2, MYH11, TGFBR2
Chamney et al 2015[24]	United Kingdom	FTAAD	14	8	3	0	1	5	36	100	AD	GEN+IMAG	ACTA2
Disabella et al 2011[25]	Italy	FTAAD	37	23	5	4	5	10	27	78	AD	GEN+IMAG	ACTA2
Disertori et al 1991[26]	Italy	FTAAD	30	13	15	0	2	2	7	na	…	IMAG	…
Dong et al 2014[27]	China	FTAAD	64	5	9	30	1	8	13	64	…	GEN+IMAG	TGFBR1
Francke et al 1995[28]	United States	FTAAD	26	15	9	0	1	9	35	67	AD	GEN+IMAG	FBN1
Gago-Diaz et al 2014[29]	Spain	FTAAD	31	3	10	13	1	6	19	60	AD	GEN	TGFB2
Gago-Diaz et al 2016[30]	Spain	FTAAD	30	12	14	3	1	10	33	88	AD	GEN	PRKG1
Guo et al 2001[31]	United States*	FTAAD	219	n/c	n/c	n/c	n/a	n/c	n/c	n/a	AD	GEN	Locus 5q13-14†
Guo et al 2007[32]	United States*	FTAAD	212	n/c	n/c	n/c	n/a	n/c	n/c	48	AD	GEN	ACTA2
Guo et al 2009[33]	United States*	FTAAD	269	n/c	n/c	n/c	n/a	n/c	n/c	49	AD	GEN	ACTA2
Guo et al 2011[34]	United States*	FTAAD/pAA	28	7	9	6	1	8	29	75	AD	GEN	Locus 12q13-14†
Guo et al 2013[35]	United States*	FTAAD	89	40	18	12	6	31	35	100	AD	GEN	PRKG1
Guo et al 2015[36]	United States*	BAV/TAA	48	10	14	15	1	7	15	44	AD	GEN	MATA2
Guo et al 2016[37]	United States*	FTAAD	65	21	22	13	6	15	23	86	AD	GEN	LOX
Hannuksela et al 2015[38]	Sweden	FTAAD	270	60	89	55	7	37	14	n/a	…	GEN+IMAG	…
Hannuksela et al 2016[39]	Sweden	FTAAD	46	n/c	n/c	n/c	1	n/c	n/c	45	…	GEN+IMAG	MYLK
Harakalova et al 2013[40]	Holland	TAAD/PDA	75	6	15	34	2	13	17	45	AD	GEN	MYH11
Hasham et al 2003[41]	United States*	FTAAD	69	4	5	39	1	16	23	75	AD	GEN+IMAG	TGFBR2
Kakko et al 2003[42]	Finland	FTAAD	213	n/c	n/c	n/c	n/a	n/c	n/c	n/a	…	GEN+IMAG	Locus 5q13-14†
Kent et al 2013[43]	United States	BAV/TAA	129	73	21	19	14	34	26	n/a	AD	GEN+IMAG	NOTCH1
Keramati et al 2010[44]	United States	FTAAD	23	10	8	0	1	12	52	90	AD	GEN+IMAG	Locus 15q21 (FBN1?)
Khau Van Kien et al 2004[45]	France	FTAAD/PDA	68	13	21	24	1	7	10	n/a	AD	GEN+IMAG	…
Khau Van Kien et al 2005[46]	France	FTAAD/PDA	87	13	26	38	1	7	8	50	AD	GEN+IMAG	MYH11
Kuang et al 2016[47]	United States*	FTAAD	40	n/c	n/c	n/c	n/a	n/c	n/c	75	AD	GEN	FOXE3
Loscalzo et al 2007[48]	United States	BAV/TAA	194	72	37	65	13	44	23	88	AD	GEN+IMAG	…
Marwick et al 1987[49]	Australia	FTADiss	17	7	5	0	1	1	6	n/a	…	IMAG	…
McManus et al 1987[50]	United States	FTADiss	19	7	9	0	1	5	26	n/a	…	IMAG	…
Milewicz et al 1998[51]	United States*	FTAAD	123	44	44	7	6	24	20	n/a	AD	GEN+IMAG	…‡

Continued

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Table 1. Continued

Study (Author/Y)	Country	NS-TAD Form	Pedigree (Patients)					Relatives Affected		Penetrance, %	Inheritance (Modality)	Type of Screening	Related Gene
			Total, No.	FDRs, No.	SDRs, No.	TDRs, No.	Probands, No.	No.	%				
Morisaki et al 2009[52]	Japan	FTAAD	47	10	6	27	3	11	23	100	…	GEN	ACTA2
Pannu et al 2005[53]	United States*	FTAAD	235	18	35	121	4	54	23	79	AD	GEN+IMAG	TGFBR2
Pannu et al 2007[54]	United States*	FTAAD	27	16	4	0	2	4	15	45	…	GEN+IMAG	MYH11
Regalado et al 2011[55]	United States*	FTAAD/ICA	231	83	64	50	13[§]	43	19	n/a	AD	GEN	ACTA2, TGFBR1, TGFBR2
Regalado et al 2011[56]	United States*	FTAAD/ICA/pAA	106	n/c	n/c	n/c	n/a	n/c	n/c	65	AD	GEN	SMAD3
Regalado et al 2011[57]	United States*	FTAAD	29	18	6	0	5	10	34	n/a	…	GEN	FBN1
Renard et al 2013[58]	Belgium	FTAAD	97	34	30	7	8	21	22	n/a	AD	GEN	ACTA2, MYH11
Robertson et al 2016[59]	Australia	FTAAD	n/c	n/c	n/c	n/c	270	341	56	n/a	…	IMAG	…
Sherrah et al 2016[60]	Australia	FTAAD	n/c	n/c	n/c	n/c	n/a	n/c	n/c	n/a	…	IMAG	…
Takeda et al 2015[61]	Japan	FTAAD	17	5	6	2	1	4	24	75	…	GEN	MYH11
Teixidó-Turà et al 2014[62]	Spain	FTAAD	36	8	5	15	1	2	6	10	…	GEN	ACTA2
Tortora et al 2017[63]	Italy	BAV/TAA	97	77	0	0	20	5	7	n/a	…	GEN+IMAG	…[‖]
Tran-Fadulo et al 2006[64]	United States*	FTAAD	153	14	45	63	3	18	12	n/a	…	GEN	…
Tran-Fadulo et al 2009[65]	United States*	FTAAD	78	31	23	7	4[¶]	26	33	70	AD	GEN	TGFBR1
Vaughan et al 2001[66]	United States*	FTAA	67	27	20	2	3	27	40	n/a	AD	GEN+IMAG	Locus 11q23.3-24[†]
Wang et al 2010[67]	United States*	FTADiss	48	n/c	n/c	n/c	n/a	n/c	n/c	50	AD	GEN	MYLK
Wang et al 2013[68]	China	FTAAD	10	7	0	0	1	1	10	n/a	…	GEN	…
Ware et al 2014[69]	United States	FTAAD	7	4	0	0	2	0	0	100	…	GEN	ACTA2
Warnes et al 1985[70]	United States	FTAAD	6	4	0	0	2	0	0	n/a	…	IMAG	…
Weigang et al 2007[71]	Germany	FTAAD	26	n/c	n/c	n/c	n/a	n/c	n/c	n/a	AD	GEN+IMAG	…
Yoo et al 2010[72]	Korea	FTAAD	20	7	7	0	1	4	20	67	AD	GEN	ACTA2
Zhu et al 2006[73]	France	FTAAD/PDA	49	n/c	n/c	n/c	n/a	n/c	n/c	44	AD	GEN+IMAG	MYH11
Ziganshin et al 2015[74#]	United States	FTAAD	27	7	11	2	1	3	11	70	AD	GEN	MYLK
Ziganshin et al 2015[74#]	United States	FTAAD	17	6	8	0	1	6	35	70	…	GEN	TGFBR1

AD indicates autosomal dominant; BAV, bicuspid aortic valve; FDRs, first-degree relatives; FTAA, familial thoracic aortic aneurysm; FTADiss, familial aortic dissection; FTAAD, familial thoracic aortic aneurysm and dissection; GEN, genetic; ICA, intracranial aneurysm; IMAG, imaging; n/a, not available; NS-TAD, nonsyndromic thoracic aortic disease; n/c, not computable; pAA, peripheral artery aneurysm; PDA, patent ductus arteriosus; SDRs, second-degree relatives; TAA, thoracic aortic aneurysm; TAAD, thoracic aortic aneurysm and/or dissection; TDRs, third-degree relatives.

*Study performed at University of Texas.

[†]Mapped loci without identified gene.

[‡]No linkage to FBN1 or TAAD2.

[§]Four probands not affected by aortic diseases (aortic aneurysm and/or dissections).

[‖]No linkage with ACTA2.

[¶]One proband not affected by aortic diseases (aortic aneurysm and/or dissection).

[#]Data of 2 different screened families obtained from the same study.

β-blockers or angiotensin receptor blockers. No correlation with the age at diagnosis, the initial aortic diameter, and the systolic or diastolic blood pressure was documented. During 10-year follow-up, 9% of newly diagnosed relatives were affected by an aortic dissection, and 18% underwent elective aortic surgery. Six relatives (of 368) originally diagnosed as unaffected (initial aortic diameter with a Z score <2) experienced a subsequent aortic dissection.[59]

Results of Imaging Tests

A total of 1039 families underwent screening for NS-TAD, with a median number of patients in each family pedigree of 48 (study range: 6–270) (Table S3). The proportion of potential eligible patients per family was 73% (study range: 50–100%), while the rate of relatives effectively screened was 54% (study range: 5–100%) (Table 2 and Table S4). FDRs, SDRs, and TDRs were variably screened throughout the studies. Twelve percent of FDRs, 24% of SDRs, and 18% of TDRs were not available for screening (Figure 1).

A total of 893 FDRs, 695 SDRs, and 670 TDRs were identified in the family pedigrees of the included studies (Table S5). Of these, a total of 910 newly affected relatives were detected, with an average among studies of 22 newly diagnosed individuals. The percentage of newly diagnosed relatives was 23% (study range: 6–56%). Newly diagnosed individuals were male in 67% of the cases (study range: 20–100%). Sudden unexplained deaths were reported in 2% of the cases (study range: 0–9%). Detailed data about rates of newly affected and screened FDRs, SDRs, and TDRs are depicted in Figure 1.

The type of aortic diseases (aneurysm and dissection rates), male preponderance rate, and age at dissection are summarized in Table 2 and Table S4. Only 1 study screened the relatives of 53 probands identified as affected by a sporadic NS-TAD form, identifying 83 of 321 newly affected relatives.[59]

Results of Genetic Tests

The techniques used in the genetic screening, the identified genes, and genetic mutations are listed in Table S8. Genetic screening was employed as the sole screening modality in 26 (49%) studies and in combination with imaging modalities in 21 (40%). A total of 14 known genes were identified as a causative mutation for NS-TADs, while 3 mapped loci without an identified gene were also found (Table 3 and Table S11). Single-gene testing was used in 24 (45%) studies, comprehensive genomic sequencing in 14 (26%), and a combination of the 2 approaches in 7 (13%), respectively (Figure 2, Tables S8 and S10).

The inheritance mode was essentially autosomal dominant (Table 1). Forty-one (79%) studies reported on the penetrance of the NS-TAD. Penetrance varied in relationship to the NS-TAD form, with an average of 67% (study range: 20–100%) and was lower in females (Table 2). The age at dissection varied according to the underlying NS-TAD form, with a mean age of presentation of 32 years for the familial thoracic aortic aneurysm and dissection forms associated with the mutations of the PRKG1 gene and of 54 years for those associated with the mutation of the MYLK gene (Figure 2 and Table 3). Ascending aortic diameters at the time of acute dissection were not reported for most of the individuals. Where this was reported, individuals affected by NS-TADs showed stratification of the diameter of the thoracic aorta (aortic root, mid ascending, or descending aorta) at dissection and in the risk of progression to dissection by genetic mutation: from <4.5 cm for FBN1, FOXE2, MILK, PRKG1, SMAD3, TGFB2, TGFBR1, and TGFBR2, to >5.5 cm for ACTA2, LOX, and MYH11, respectively (Figure 2, Table S10). The identified NS-TAD forms presented specific characteristics based on the causative genetic mutation (Tables 1 and 3, Table S10, and Figure S2).

Extra-Aortic Manifestations of NS-TAD

Concomitant cardiovascular diseases were diagnosed in 11% of the relatives undergoing screening, while concomitant physical abnormalities were observed in 18% of the cases. Full details of all described external physical features and abnormalities of other organ systems are reported in Table S6.

Resource Use and Cost-Effectiveness

No information about resource use and the cost-effectiveness of screening program in relatives of patients with NS-TAD was reported in any of the identified studies. No studies address the psychological effect of screening in patients and their relative or its impact on quality of life of these families.

Discussion

Main Findings

The present study has identified an area of unmet clinical need with respect to screening of relatives of patients with NS-TAD: familial NS-TADs occur more frequently than previously recognized, affecting ≈30% of relatives with a male predominance (3:1). These are primarily inherited as single gene mutations, expressed in an autosomal dominant pattern with incomplete penetrance, which demonstrate variable expression with respect to age of presentation, sex, aneurysmal location, and aortic diameter before dissection. The risk of acute aortic syndrome is determined by the underlying

Table 2. Details of Newly Diagnosed Diseases of the Thoracic Aorta in the Screened Relatives

Study (Author/Y)	No. of Relatives Screened	Patients Affected* (Aortic Aneurysm+Aortic Dissection)				Sudden Death (Unexplained)		Aortic Aneurysm*		Aortic Dissection*			
		No.	%	Male	%	No.	%	No.	%	No.	%	Age at Dissection, y	Range (Age, y)
Barbier et al 2014[22]	13	9	23	3	33	n/a	…	8	89	1	11	58	n/a
Bee et al 2012[23]	32	21	39	16	76	n/a	…	21	100	0	0	…	…
Chamney et al 2015[24]	6	6	43	4	67	0	0	3	50	3	50	49±10.4	37–55
Disabella et al 2011[25]	29	15	41	8	53	1	3	6	40	9	60	49.3±16.3	29–73
Disertori et al 1991[26]	14	4	13	4	100	n/a	…	2	50	2	50	46±2.8	44–48
Dong et al 2014[27]	39	9	14	7	78	1	2	6	67	3	33	39±6.9	35–47
Francke et al 1995[28]	23	10	38	6	60	n/a	…	8	80	2	20	55±14.1	45–65
Gago-Diaz et al 2014[29]	12	7	23	5	71	n/a	…	5	71	2	29	37.5±4.9	34–41
Gago-Diaz et al 2016[30]	14	11	37	6	55	1	3	5	45	6	55	34.2±12.9	15–48
Guo et al 2001[31]	121	73	33	47	64	n/a	…	n/a	…	n/a	…	…	…
Guo et al 2007[32]	130	53	25	33	62	n/a	…	8	15	45	85	37.3±13.9	13–67
Guo et al 2009[33]	163	66	25	39	59	n/a	…	n/a	…	n/a	…	…	…
Guo et al 2011[34]	18	9	32	9	100	n/a	…	8	89	1	11	32	n/a
Guo et al 2013[35]	39	37	42	16	43	n/a	…	15	41	22	59	31.1±10.3	17–51
Guo et al 2015[36]	34	8	17	5	63	1	2	8	100	0	0	…	…
Guo et al 2016[37]	21	21	32	17	81	2	3	17	81	4	19	44.8±15.1	25–60
Hannuksela et al 2015[38]	106	44	17	32	73	0	0	27	61	17	39	48†	15–75
Hannuksela et al 2016[39]	19	6	13	4	67	0	0	0	0	6	100	53.2±21.1	23–75
Harakalova et al 2013[40]	40	15	20	10	67	3	4	4	37	11	73	46.6±19.5	18–70
Hasham et al 2003[41]	52	17	25	14	82	n/a	…	9	53	8	47	45.4±21.5	14–72
Kakko et al 2003[42]	115	39	18	25	64	n/a	…	26	67	13	33	53.2±15.5	26–80
Kent et al 2013[43]	93	48	37	37	77	n/a	…	n/a	…	n/a	…	…	…
Keramati et al 2010[44]	15	13	57	6	46	n/a	…	10	77	3	23	n/a	n/a
Khau Van Kien et al 2004[45]	49	8	12	6	75	3	4	4	50	4	50	n/a	n/a
Khau Van Kien et al 2005[46]	78	8	9	6	75	2	2	4	50	4	50	n/a	n/a
Kuang et al 2016[47]	16	11	28	11	100	n/a	…	0	0	11	100	44.3±22.6	9–88
Loscalzo et al 2007[48]	138	57	29	42	74	n/a	…	n/a	…	n/a	…	…	…
Marwick et al 1987[49]	4	2	12	1	50	0	0	0	0	2	100	26.5±3.5	24–29
McManus et al 1987[50]	8	6	32	5	83	n/a	…	0	0	6	100	33.5±14.9	22–62
Milewicz et al 1998[51]	n/a	30	24	18	60	9	7	12	40	18	60	42.9±11.3	22–62

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Table 2. Continued

Study (Author/Y)	No. of Relatives Screened	Patients Affected* (Aortic Aneurysm+Aortic Dissection)				Sudden Death (Unexplained)		Aortic Aneurysm*		Aortic Dissection*			
		No.	%	Male	%	No.	%	No.	%	No.	%	Age at Dissection, y	Range (Age, y)
Morisaki et al 2009[52]	9	14	30	10	71	5	11	3	21	11	79	36.8±10.1	25–52
Pannu et al 2005[53]	72	58	25	39	66	n/a	…	27	46	32	54	46.1±16.3	14–73
Pannu et al 2007[54]	23	6	22	4	67	n/a	…	1	17	5	83	45±8.8	37–56
Regalado et al 2011[55]	12	52	23	35	67	7	3	9‡	17	43†	83	50.8±13.7	25–76
Regalado et al 2011[56]	36	23	22	14	61	1	1	9	39	14	61	42§	25–54
Regalado et al 2011[57]	11	15	52	8	53	n/a	…	7	47	8	53	32.3±9.9	18–50
Renard et al 2013[58]	29	29	30	16	55	3	3	14	48	15	52	48.0±21.2	33–63
Robertson et al 2016[59]	581	486	38	266	72	n/a	…	370	76	116	24	50±13	n/a
Sherrah et al 2016[60]	119‖	n/a	n/a	68	76	n/a	…	n/a	…	n/a	…	n/a	…
Takeda et al 2015[61]	9	5	29	4	80	0	0	1	20	4	80	47.8±16.6	32–70
Teixidó-Turà et al 2014[62]	10	3	8	2	67	1	3	1	33	2	67	46.5±12	38–55
Tortora et al 2017[63]	77	25	26	61	79	n/a	…	25	100	0	0	…	…
Tran-Fadulo et al 2006[64]	9	21	14	7	33	0	0	4	19	17	81	32.0±12.3	16–55
Tran-Fadulo et al 2009[65]	49	29	37	17	59	0	0	15	52	14	48	n/a	14–62
Vaughan et al 2001[66]	63	30	45	8	27	n/a	…	n/a	…	n/a	…	…	…
Wang et al 2010[67]	21	10	21	5	50	2	4	0	0	10	100	54.3±20.8	16–78
Wang et al 2013[68]	8	2	20	2	100	0	0	1	50	1	50	n/a	n/a
Ware et al 2014[69]	7	2	20	2	100	0	0	0	0	2	100	17	…
Warnes et al 1985[70]	2	2	33	2	100	0	0	0	0	2	100	35.0±18.4	22–48
Weigang et al 2007[71]	23	9	35	5	56	0	0	3	33	6	67	32‡	18–47
Yoo et al 2010[72]	6	5	25	1	20	0	0	0	0	5	100	32.5±12.9	20–46
Zhu et al 2006[73]	49	8	16	7	88	n/a	…	5	63	3	38	n/a	n/a
Ziganshin et al 2015[74¶]	15	4	15	2	50	n/a	…	1	25	3	75	n/a	n/a
Ziganshin et al 2015[74¶]	15	7	41	4	57	n/a	…	4	57	3	43	n/a	n/a

n/a indicates not available.
*Percentage calculated in the family pedigree (as per protocol).
†Median available only.
‡Data available from 4 families only (TAA288, TAA062, TAA549, TAA395).
§Mean available only.
‖Comprehensive of patients affected by bicuspid aortic valve.
¶Data of 2 different screened families obtained from the same study.

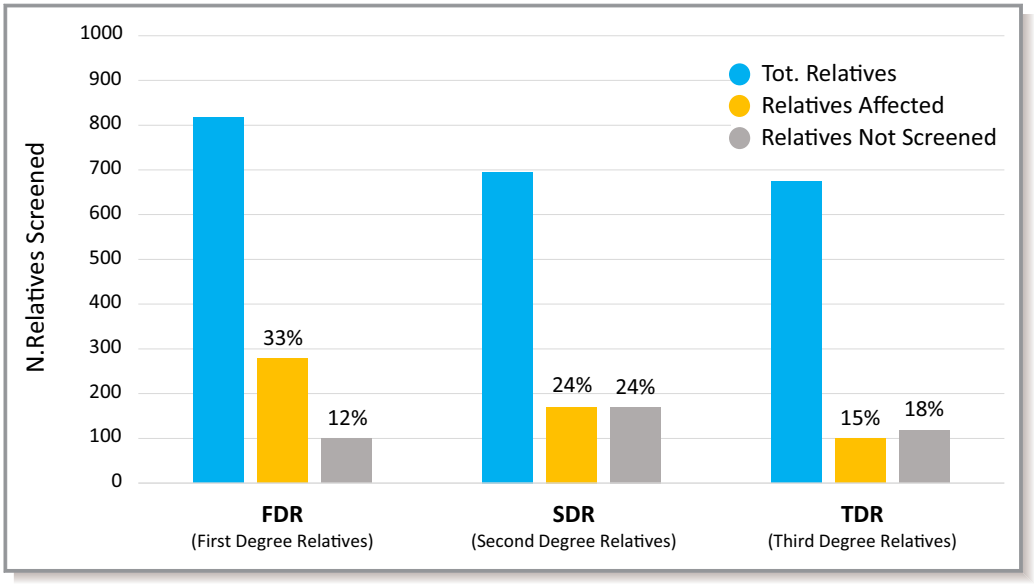

Figure 1. Relatives screened in the studies included in the systematic review. Details for newly affected and not screened individuals are provided for first-, second-, and third-degree relatives (FDRs, SDRs, and TDRs, respectively).

genetic mutation and this risk extends not only to FDRs but also to SDRs and TDRs of patients affected by NS-TADs. There is an overlap between nonsyndromic and syndromic TADs for some genetic mutations, as well as concomitant cardiovascular pathology in over 10% of screened patients. The review also identified knowledge gaps with respect to the predictive accuracy of commonly used screening tests across NS-TAD populations, the optimal structure and extent of a screening program across families, and the effectiveness of a screening program with respect to clinical outcomes or cost.

Clinical Implications

Nonsyndromic aortopathies have poor prognosis if untreated and the lack of relevant physical features precludes identification based on a clinical characteristics alone.[7,75] As a consequence, NS-TADs are asymptomatic, alerting clinicians to the underlining aortopathy only when sudden death or an acute aortic dissection occurs.[7,19,72,75] This review indicates that routine screening and surveillance programs in relatives of patients affected by NS-TADs, similar to those of syndromic TAD, are likely to identify significant numbers of patients with asymptomatic NS-TAD.[4,5,76,77] The overlap in genetic mutations between NS-TAD and syndromic TAD identified in the review further support this assertion. It follows that diagnosis, surveillance, and treatment of NS-TADs before clinical presentation, as is the standard of care for syndromic TAD, is likely to reduce premature deaths. The findings of this article also indicate that current guidelines which recommend treatment based predominantly on the aortic diameter are likely to result in the undertreatment of NS-TADs.[4,5] Specifically, subtypes of NS-TADs attributed to specific genetic mutations may progress to aortic dissection without aneurysm formation.[78] Here, the treatment of affected relatives stratified by NS-TAD subtype and genetic abnormality are likely to result in further clinical benefits (Figure 2).

In addition to defining an area of unmet need, the review has identified important knowledge gaps with respect to screening. Specifically, the diagnostic accuracy of existing screening tests, the optimal screening program, and the clinical, societal, or economic benefits of such a screening program in the relatives of patients with sporadic or familial NS-TAD are unclear. Current guidelines for the diagnosis and treatment of aortic diseases do not specify the details of what screening tests should be used (Table S11).[4,5,77] The 2014 European Society of Cardiology guidelines recommend investigating FDRs by genetic counseling for family investigation and molecular testing, with a 5-year interval screening until diagnosis (clinical or molecular) is established or ruled out (class I, level of evidence C).[5] The corresponding 2010 American guidelines suggest aortic imaging screening for FDRs along with counseling and testing whether a specific mutant gene (FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) is identified in the affected probands (class I, level of evidence C).[4] These recommendations are based on opinion of the experts and small group studies only.[4,5] Importantly, specific testing schedules, the requirement for screening of SDRs and TDRs, the need for sequencing of other less-common mutant genes, the optimal screening interval and modality, or the need to investigate the entire arterial tree

Table 3. Genetic Mutations and Correlations With Age and Size at Dissection*

Study (Author/Y)	Patients Affected (Aneurysm+Dissection)		Aortic Dissection								
	No.	%	Patients, No.	Patients, %	Male No.	Male, %	Age at Dissection, y	Range, y	Size at Dissection, mm	Range, mm	Patients Available for Analysis
ACTA 2											
Chamney et al 2015[24]	6	43	3	50	3	100	49±10.4‖	37–55	n/a	…	…
Disabella et al 2011[25]	15	41	9	60	5	56	49.3±16.3‖	29–73	59.1±22.3‖	41–95	7
Guo et al 2007[32]	53	25	45	85	23	51	37.3±13.9‖	13–67	61.1±15.0‖	45–100	12
Morisaki et al 2009[52]	14	30	11	79	9	82	36.8±10.1‖	25–52	n/a	…	…
Renard et al 2013[58]	26	32	13	79	7	54	40.7±15.4‖	27–70	n/a	…	…
Ware et al 2014[69]	2	20	2	100	2	100	17	…	53±7.1‖	48–58	2
Yoo et al 2010[72]	5	25	5	100	1	20	32.5±12.9‖	20–46	35	…	1
FBN1											
Francke et al 1995[28]	10	38	3	30	2	67	55±14.1‖	45–65	n/a	…	…
Regalado et al 2016[37]	15	52	8	53	4	50	32.3±9.9‖	18–50	44	…	1
FOXE3											
Kuang et al 2016[47]	11	28	11	100	11	100	44.3±22.6‖	9–88	n/a	…	…
LOX											
Guo et al 2016[37]	21	32	4	19	4	100	44.8±15.1‖	25–60	n/a	…	…
MYH11											
Harakalova et al 2013[40]	15	20	10	67	7	70	46.6±19.5‖	18–70	58.5±17.3‖	44–65	4
Khau Van Kien et al 2005[46]	8	9	4	50	3	75	n/a	…	n/a	…	…
Pannu et al 2008[56]	6	22	5	83	4	80	45±8.8‖	37–56	44	…	1
Renard et al 2013[58]	3	20	2	83	1	50	48.0±21.2‖	33–63	n/a	…	…
Takeda et al 2015[61]	5	29	4	80	4	100	47.8±16.6‖	32–70	n/a	…	…
Zhu et al 2006[73]	8	16	3	38	2	67	n/a	…	37.3±7.8†	n/a	2
MYLK											
Hannuksela et al 2016[39]	6	13	6	100	5	83	53.2±21.1‖	23–75	47.5±0.7‖	47–48	2
Wang et al 2010[66]	10	21	10	100	5	50	54.3±20.8‖	16–78	40	…	1
Ziganshin et al 2015[74]	4	15	3	75	1	33	n/a	…	n/a	…	…
PRKG1											
Gago-Diaz et al 2016[30]	11	37	6	55	3	50	34.2±12.9‖	15–48	43±1.4‖	42–44	2
Guo et al 2013[35]	37	42	22	59	10	45	31.1±10.3‖	17–51	47±14.1‖	37–57	2

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Table 3. Continued

Study (Author/Y)	Patients Affected (Aneurysm+Dissection)		Aortic Dissection								
	No.	%	Patients, No.	Patients, %	Male No.	Male, %	Age at Dissection, y	Range, y	Size at Dissection, mm	Range, mm	Patients Available for Analysis
SMAD3											
Regalado et al 2011[56]	23	22	14	61	n/a	n/a	42‡	25–54	50	50	1
TGFB2											
Gago-Diaz et al 2014[29]	6	19	2	33	2	100	37.5±4.9‖	34–41	n/a	…	…
TGFBR1											
Dong et al 2014[27]	9	14	3	33	3	100	39±6.9‖	35–47	51.3±17.9‖	40–72	3
Tran-Fadulo et al 2009[64]	29	37	14	48	10	71	25.6±14.3 (male)§ 38.6±9.7 (female)	14–62	90.6±42.7‖	65–140	2
Ziganshin et al 2015[74]	7	41	3	43	2	67	n/a	…	n/a	…	…
TGFBR2											
Hasham et al 2003[41]	17	25	8	47	6	75	45.4±21.5‖	14–72	n/a	…	…
Pannu et al 2005[53]	59	25	32	54	22	69	46.1±16.3‖	14–73	n/a	…	…
Tran-Fadulo et al 2009[65]	n/a	…	n/a	…	n/a	…	42.6±17.8 (male)§ 51.3±17.1 (female)	n/a	44±2.8‖	42–46	2

n/a indicates not available.

*No data available for patients affected by aortic dissection regarding the genes NOTCH1 (reference 22) and MFAP5 (reference 1), and patients with MAT2A mutation did not experience aortic dissections (reference 15).

†Data available for dissection of the descending thoracic aorta only.

‡Average age onset of dissection as presented by the authors.

§Derived from the entire cohort of patients with TGFBR1 and TGFBR2 mutations.

‖Expressed as mean±SD.

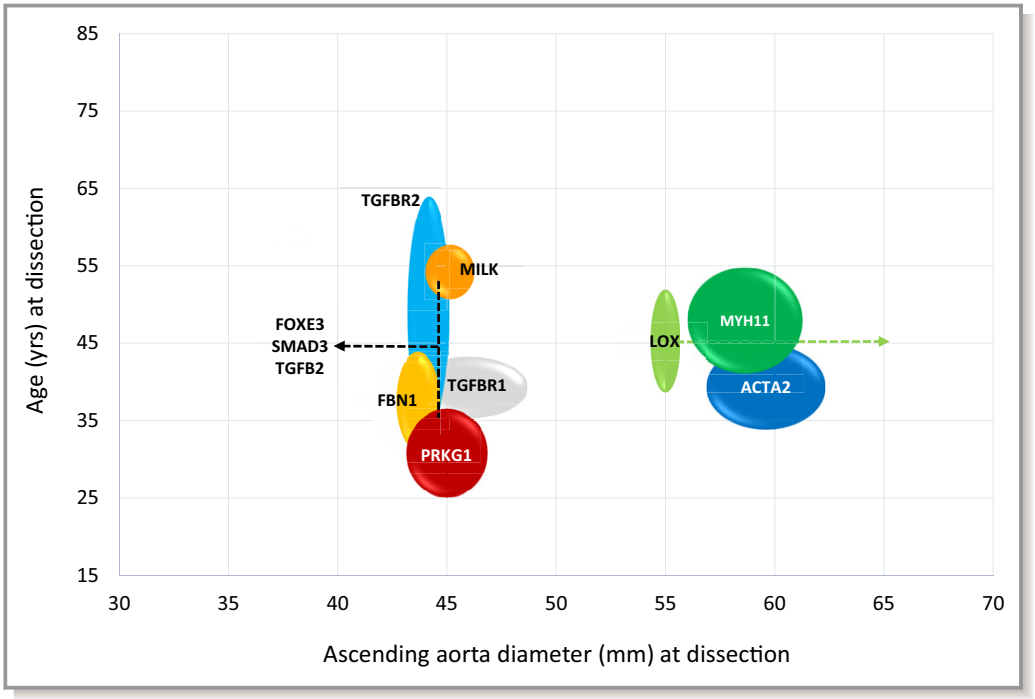

Figure 2. Schematic representation of genetic mutations with age and ascending aorta diameter at dissection. The widening of the circles/lines represents SD in terms of age and diameters. Data are obtained from studies included in the systematic review. No numerical data were available for patients affected by aortic dissection regarding the genes NOTCH1 and MFAP5, and patients with MAT2A mutation did not experience aortic dissections.[1,36,43]

other than the thoracic aorta are not specified.[4,5] The results of the current study suggest that FDRs, SDRs, and possibly TDRs should be offered screening for TAD. Clarification of the family history regarding the location of the aortic disease, the specific nature of "sudden deaths," or the presence of other concomitant cardiovascular disorders during clinical examination should represent the initial step of screening.[75] Our results also suggest that genetic testing and cardiac imaging with at least TTE should be offered to all FDRs and SDRs of patients with suspected NS-TADs. Mutation carriers should undergo further imaging (MRI or CT scan), focusing on thoracic aorta and/or other arterial trees based on the causative gene mutation.[22–74] For example, ACTA2-mutation carriers should be monitored for coronary artery disease and occlusive cerebrovascular disease, in addition to the currently recommended routine imaging tests.[32] We suggest that complete aortic imaging at initial diagnosis and at 6 months for patients with a confirmed genetic aortopathy (eg, FBN1, FOXE3, MFAP5, MYLK, PRKG1, SMAD3, TGFB2, TGFBR1, and TGFBR2) should be obtained to establish whether aortic enlargement is occurring.[4,74] The final clinical management of patients with a specific gene mutation could be modified on the basis of these data, enabling personalized treatment that is independent of the native aortic diameters.[4,5,41,50] Only relatives in whom a causal mutation is excluded and the aortic size is within recommended diameters should reasonably undergo clinical and/or imaging screening every 2 to 5 years, until diagnosis is confirmed or ruled out.[5,76] The appropriate temporal interval for follow-up imaging, as well as the starting age for aortic surveillance, are also poorly defined. Generally, patients with NS-TAD are diagnosed on average 10 years older than patients affected by syndromic aortopathies, being also characterized by a lower annual aortic dilatation progression (0.5–0.7 mm/y).[59,60] It therefore seems reasonable to initiate the screening 15 to 10 years earlier than first aneurysm or when dissection or sudden death is recorded within the family.[60,79] A screening pathway based on these observations is proposed in Figure 3.

There are several additional factors that may influence our proposed screening algorithm. First, variable penetrance, which often characterizes NS-TAD forms, is a potential confounder. This results in intrafamilial variability, which is evident not only with reference to the aortopathy itself (severity, age of onset), but also with regard to other phenotypic manifestations.[65–81] The presence of associated features is certainly suggestive of having inherited the aortic condition along with the predisposition to the aortopathy, but the absence of these associated features does not eliminate the risk of having an underlying aortopathy. Second, women often demonstrate a lower lifetime risk of aortopathy,

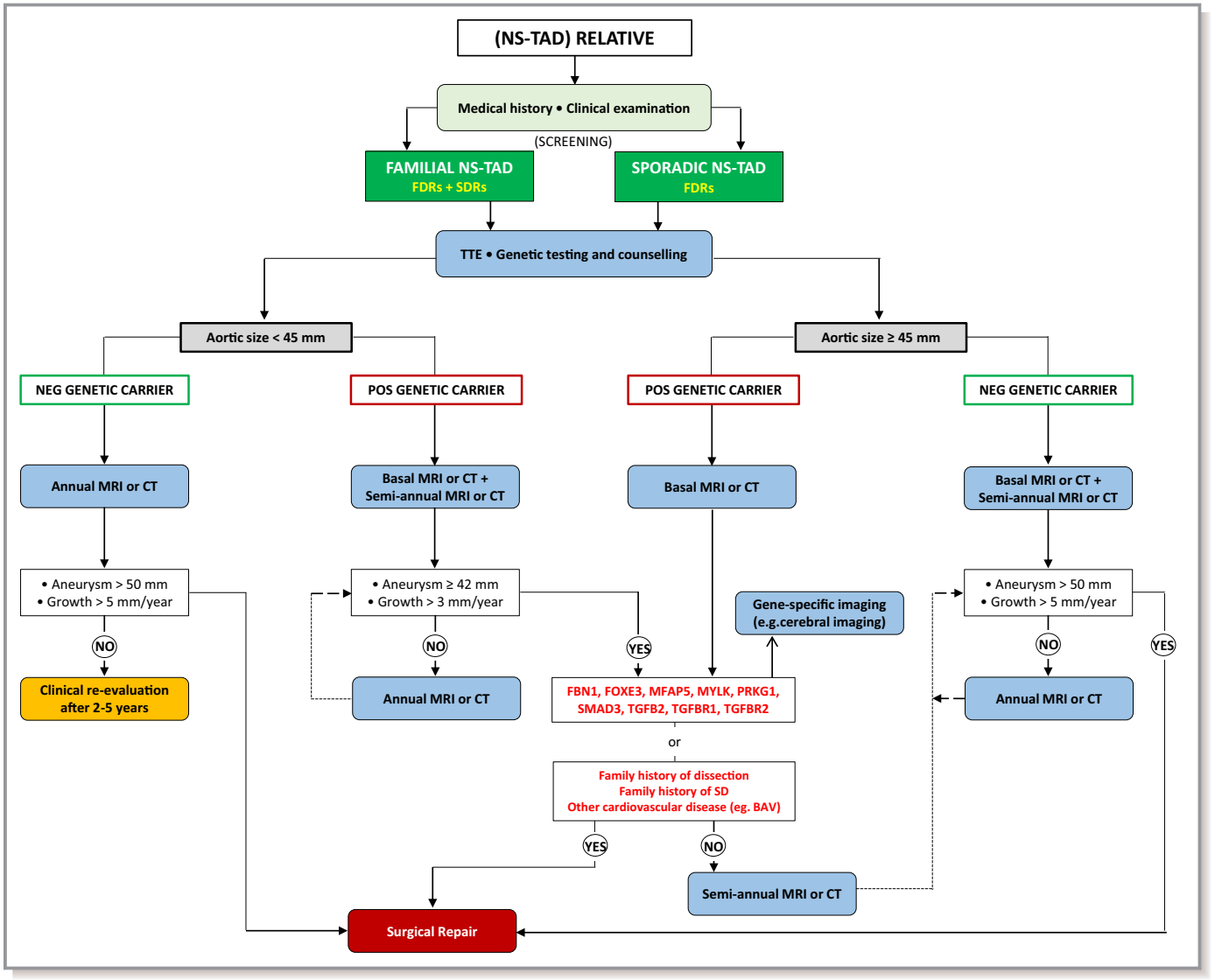

Figure 3. Proposed flow chart for a dedicated screening program for relatives of patients affected by nonsyndromic diseases of the thoracic aorta based on the authors' extensive literature review. The figure represents the best judgement of the authors. BAV indicates bicuspid aortic valve; CT, computed tomography; FDRs, first-degree relatives; MRI, magnetic resonance imaging; NS-TAD, nonsyndromic thoracic aortic disease; SDRs, second-degree relatives; TTE, transthoracic echocardiogram.

developing the condition at a later age than men.[81] This phenomenon, known as sexual dimorphism, explains the apparent paradox of an affected teenager with an affected maternal grandfather but an unaffected mother with normal echocardiographic features. Third, the age at onset of the aortopathy may be important in the natural history of the disease. Ma et al[82] recently demonstrated that age at onset of aortic dissection is lower in families with a positive history for aortic dissection, therefore suggesting a prompt and more aggressive screening pathway in these families. A positive family history with an aortopathy occurring at younger ages confers a significantly increased risk of developing a new dissection in apparently unaffected family members.[81] The above findings are all important in guiding the proper screening and surveillance strategies.

Study Limitations

The most important limitation of the review is the uncertainty regarding the likely yield of new cases if a screening program were to be implemented. The studies identified in our searches were predominantly studies of familial aortopathy, and the prevalence of TAD in these populations will not reflect that for NS-TAD overall. Conversely, sporadic NS-TAD, which constitutes the majority (80%) of all cases also has a genetic component.[7] Roberston et al[59] investigating 321 NS-TAD probands who had no family history of TAD identified 27% of newly affected relatives. It is likely that these patients are carriers of a de novo mutation, making these "sporadic" patients founders of a new nonsyndromic aortopathy. For example, recent studies have identified gene deletions and uniparental disomy, and genetic variations in LRP1 and ULK4

in sporadic NS-TAD.[83] This suggests that the relatives of patients affected by both familial and sporadic NS-TADs may benefit from screening. It also argues for use of nontargeted genetic screening tests such as exome or whole genome sequencing that will detect de novo or as-yet unrecognized common mutations. A second limitation is that there is currently no evidence to inform secondary prevention or intervention strategies in newly diagnosed NS-TAD, particularly where the aorta is phenotypically normal. Although the evidence presented supports the routine implementation of combined imaging and genetic testing in relatives of patients with NS-TAD, no study has proven that stratified treatment, independent of the native aortic diameter, will save lives. However, the stratified treatment of syndromic TAD is common practice, as this is known to prevent deaths from aortic disease. We suggest that the results of this review support the extension of similar programs to all patients with TAD. To address these limitations, we propose that further research should first establish the true prevalence of genetic abnormalities and phenotypic disease diagnosed by screening (genetic testing and imaging) all FDRs and SDRs of patients with both familial and sporadic NS-TAD. Further studies will be required to address uncertainty with respect to effectiveness, psychological impact, and the costs of lifelong screening in these groups. Finally, the heterogeneity of the included studies, the large period of publication across 3 decades, and the familial-based approach have limited our ability to analyze the impact of region or ethnicity in the risk of aortopathies and the related screening strategy.

Conclusions

The findings of this review support routine imaging and genetic testing of relatives of patients with nonsyndromic aortopathies. The evidence suggests that screening of FDRs and SDRs of patients affected by familial NS-TAD and FDRs of those affected by sporadic NS-TADs will result in significant numbers of patients with otherwise undiagnosed disease. Personalized screening programs determined by the subtype of NS-TAD and its related genetic mutation have the potential to benefit these patients. However, the diagnostic yield of available screening tests is unclear, as are the details of a screening program, and there is no existing evidence that routine screening and stratified treatment will have clinical or economic benefits. Further studies are required to address these knowledge gaps.

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Author Contributions

Mariscalco and Debiec had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Mariscalco, Debiec, Samani, and Murphy. Acquisition of data: Mariscalco and Debiec. Analysis and interpretation of data: Mariscalco, Debiec, Samani, and Murphy. Drafting of the article: Mariscalco, Elefteriades, Samani, and Murphy. Critical revision of the article for important intellectual content: Mariscalco, Debiec, Elefteriades, Samani, and Murphy. Article supervision: Mariscalco, Elefteriades, Samani, and Murphy. Statistical analysis: Mariscalco.

Disclosures

Mariscalco declares support from Vascutek, an aortic prosthesis manufacturer, to attend scientific meetings. Murphy declares support from BHF chair of cardiac surgery, Vascutek for attendance at scientific meetings and financial support for educational activities. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

A Systematic Review of Screening of Relatives of Patients with Non-Syndromic Thoracic Aortic Diseases

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1.2. Conflict of interest

None

1.3. Founding Sources/Sponsor

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1.8. Keywords

Systematic review; aorta, thoracic; aortic aneurysms; aortic dissection; relatives; siblings; pedigree; humans; screening; echocardiography; sporadic thoracic aorta; cardiac surgery.

2. GLOSSARY/ABBREVIATIONS

BAV	Bicuspid Aortic Valve
CT	Computed Tomography
LDS	Loeys-Dietz Syndrome
MFS	Marfan Syndrome
MRI	magnetic Resonance Imaging
NS-TAD	Non-syndromic Thoracic Aortic Disease
OMIN	Online Mendelian Inheritance in Man
TAA	Thoracic Aortic Aneurysms
TAD	Thoracic Aortic Disease
TADA	Thoracic Aortic Acute Dissection
TEVAR	Transaortic Endovascular Aortic repair
TOE	Transoesophageal Echocardiogram
TTE	Transthoracic Echocardiogram

3. BACKGROUND AND RATIONALE

3.1. Rationale

Recent guidelines on diagnosis and management of thoracic aorta disease (TAD) have identified a knowledge gap with respect to the most effective screening modality for relatives of patients affected by non-syndromic TAD. Previous research has established a specific and clear screening pathway for syndromic TAD forms, including Marfan (MFS) and Loeys-Dietz (LDS) syndromes, and other similar connective tissue diseases. Considering the incidence of NS-TAD and the impact of prompt diagnosis in improving clinical outcomes in TAD, we attempted to analyse the existing evidence that relates to screening modality and programs in relatives of patients affected by non-syndromic TAD.

3.2. Key points

Thoracic aortic disease is a term that essentially refers to an interrelated collection of pathologies that include thoracic aortic aneurysms (TAA) and aortic dissections (TADA).[1,2] TAA is often silent and commonly present as life-threatening emergencies, referred to as acute aortic syndromes.[1,2] In the United Kingdom (UK), over 6,500 deaths are attributable to TAD every year, and this number is increasing.[3,4] Attempts to formulate consensus statements and relevant guidelines have identified significant gaps in the knowledge with respect to the pathogenesis, appropriate management of, and configuration of clinical services for optimal treatment of aortic disease. This results in high variation in the diagnosis and management approach and regional differences in the quality of care and outcomes.[1,2,4] In particular methodology and modalities for genetic or imaging familial screening sof relatives of patients with non-syndromic forms of TAD (NS-TAD) are not well established.[1,2] To address this knowledge gap, we propose to undertake a systematic review of the existing literature that relates to genetic and/or imaging screening undertaken in relatives of patients with NS-TAD (diagnosed and/or operated on). Secondary aims are also to determine the effectiveness of screening in relatives of NS-TAD patients, and to catalogue existing evidence on genetic association in non-syndromic TAD.

3.3. Description of the condition and the intervention

3.3.1. Epidemiology and outcomes of TAD

The term “thoracic aortic disease” includes a wide range of aortic diseases with variable clinical presentations and prognosis. The Global Burden of Disease 2010 project demonstrated that the overall global death rate from aortic aneurysms and aortic dissection increased from 2.49 per 100000 to 2.78 per 100000 inhabitants between 1990 and 2010, with higher rates for men.[5] At the same time, admissions for thoracic aortic aneurysms have increased from 4.4 to 9.0 per 100000 in the UK, mainly due to an increase in proportion of elderly patients, over 75 years of age.[3] The epidemiology of TAD is difficult to establish since aortic diseases may be diagnosed after a long period of subclinical development or they may have an acute fatal presentation. In addition, the natural history of TAD remains poorly understood, and errors in the diagnostic process may account for deaths otherwise attributed to other diseases such as myocardial infarction or pulmonary embolism. TADs are usually asymptomatic until an acute complication occurs, requiring a prompt diagnosis and treatment in specialized centres. Management of TAD is complex and dictated by the size, extent and location of the disease condition as well as the underlying pathology (aneurysm or dissection). Options include conservative medical therapy (e.g. oral hypotensive agents such as beta blockers, ace-inhibitors, diuretics or statins) open surgical intervention, thoracic endovascular aortic repair (TEVAR), or hybrid procedures including epiaortic vessel debranching.[1,2]

Early and late results also vary across centres and countries. In Europe and the wider world, mortality rates for operated type A acute aortic dissection range from 12% to 42%.[4,6-8] However, in some high-volume USA centres the mortality rate is lower, ranging from to 2 to 10%.[9,10] On the other hand, hospital mortality from elective nondissection surgery on the thoracic aorta ranges from 5% to 10%.[11] For patients suffering from an acute type B aortic dissection, mortality rates for medical treatment approach, endovascular and open surgical repair range from 3% to 20%.[12,13] Table 1 summarizes early and long-term mortality for treated TADs.

Table 1. Epidemiology and outcomes of treated TAD							
	Operation/ Disease	**Hospital mortality (30-day)**	**Mortality (Kaplan-Meier)**	**Some complications**	**Description**	**Re-op**	**Ref**
1	Bentall procedure: Composite valve & graft replacement of ascending aorta and aortic valve	0%	9.9%±4.8% at 8 years	9% post-op Thromboembolic event	MFS, n=56, mean age 38	2%	(14)
		2.6%	10.4% ± 3.4% at 10 years	3.7% post-op Thromboembolic event	N= 195, mostly annuloaortic ectasia (54.4%), ascending aortic aneurysm 26.2%		(15)
2	Separate ascending aorta and aortic valve replacements	2%	31% at 5 years		N=50, mean age 65	0	(16)
3	Valve-sparing aortic root reconstruction	0%	0% at 8 years	1% post-op Thromboembolic event	MFS, n=84, mean age 29	6%	(14)
		1.3%	17% ±5% at 8 years	3% post-op Thromboembolic event	N= 151, Aortic root aneurysms	1%	(17)
4	Ascending aorta alone	0%	0% at 5 years		N = 21	0	(16)
5	Acute Type A Aortic Dissection (operated)	26 %	n.a.	The risk of death after surgical repair of acute aortic dissection is strongly influenced by associated stroke, mesenteric ischemia, renal failure, and myocardial ischemia	N=208	n/a	(18)
		22%	5.1% ±1.2% at 5 years 11.9%±2.6 % at 10 years		N=487	n/a	(19)
	Acute Type A Aortic Dissection (not operated)	58%	n/a		N=81	n/a	(18)
	Type B Aortic Dissection (operated)	31.4%	n/a		N=35	n/a	(18)
	Type B Aortic Dissection (not operated)	10.7%	n/a		N=140	n/a	(18)
6	Arch replacement	8.9% (elective 6.0%)	n/a	stroke rate 8.4% (elective 6.9%)	N= 347, (elective 232)	n/a	(20)
7	Descending aorta replacement	7.1%	13% at 1 year 28% at 5 years	unruptured	N=11565	n/a	(21)
		45.6%	74% at 5 yrs	ruptured	N=1307	n/a	(21)
		6.1%	18% at 1 year 62% at 5	Although perioperative mortality is lower with TEVAR, Medicare	N=2433	n/a	(55)

			years	patients selected for TEVAR have worse long-term survival than patients selected for open repair.			
8	TEVAR to descending thoracic aorta (unruptured)	28.4%	77% at 5 years	Although perioperative mortality is lower with TEVAR, Medicare patients selected for TEVAR have worse long-term survival than patients selected for open repair.	N=299	n/a	(21)
9	TEVAR to descending thoracic aorta (ruptured)						

3.3.2. Forms of TAD

Currently TAD can be subdivided in two main entities:

1) Syndromic TAD
2) Non-syndromic TAD (NS-TAD)

Up to 20% of individuals with TAD who do not present pathognomonic features of syndromic forms (especially MFS or LDS), have a family history of TAA and/or TADA.[22] Syndromic forms of TAD are associated with abnormalities of other organs, while those non-syndromic present manifestations limited to the thoracic aorta only. NS-TAD includes two distinct sub-groups: the familial (more than one family member is affected) and the sporadic TAD forms.[22] Table 2 summarizes syndromic and non-syndromic forms of TAD.[23]

Table 2. Syndromic and non-syndromic aneurysms conditions

Syndromic Aneurysms Conditions	Non-syndromic Aneurysm Conditions
MFS (Marfan syndrome)	FTAAD
LDS (Loeys-Dietz syndrome)	
Vascular Ehlers-Danlos syndrome	Familial TAA
Shprintzen-Goldberg syndrome	
Aneurysms-osteoarthritis syndrome	BAV with thoracic aortic aneurysm
Cutis laxa with aneurysm	

A genetic predisposition to the development of TAD in non-syndromic forms has been documented in 19% of patients, and patients with familial TAD are younger at the time of diagnosis that those with sporadic forms, but older when compared to syndromic TAD forms.[22] Previous studies have also suggested that 20% of NS-TAD patients referred for surgery have first-degree relatives similarly affected.[22,24]

In majority of patients the familial NS-TAD is inherited as an autosomal-dominant disorder with decreased penetrance and variable expression. Several genes have been demonstrated to be involved NS-TAD (Table 3).[23,25,26]

3.3.3. Imaging modality for screening TAD

Imaging techniques play a crucial role in the diagnosis, follow-up and management of TAD. Ultrasound, including transthoracic (TTE) and transoesophageal (TOE) echocardiograms, computed tomography (CT) and magnetic resonance (MR) can be used for the assessment of aneurysms and dissections located in the different segments of the thoracic aorta. All these imaging modalities have their strengths and limitations, and no single imaging modality has a perfect resolution (Table 4).[1,2,27]

The preferred imaging modality for screening of TAD has not yet been recommended in the international guidelines (ESC, AHA), and a variable combinations of imaging modalities at baseline and during follow-up have been reported. In addition, relationship between genetic and imaging screening modalities has not been elucidated in relatives of patients with NS-TAD.[1,2]

Table 3. genes associated with NS-TAD forms	
Gene (protein)	**OMIN N.**
Extracellular Matrix proteins	
FBN1 (fibrillin-1)	154700
COLA3A1 (Collagen 3 α-1)	130050
LOX (lysyl oxidase)	Unassigned
MFAP5 (microfibrillar associated protein 5)	616166
TGF-β pathway	
TGFBR1 (transforming growth factor-β receptor 1)	609192
TGFBR2 (transforming growth factor-β receptor 2)	610168
SMAD2 (SMAD family member 2)	Unassigned
Cytoskeletal/smooth muscle contraction apparatus proteins	
ACTA2 (α-smooth muscle actin)	611788
MYH11 (smooth muscle myosin)	132900
MYLK (myosin light chain kinase)	613780
PRKG1 (protein kinase, cGMP-dependent, type I)	615436
Neural crest migration	
NOTCH1 (notch1)	109730
Unknown	
MAT2A (methionine adenosyl-transferase II, α)	Unassigned
FOXE3 (forkhead box 3)	Unassigned

3.3.4. Genetic screening for TAD

Establishing a specific genetic cause of NS-TAD is of paramount importance for defining the most appropriate management for the relatives of affected patients. Risk assessment and surveillance as well recommendations for specific medical and surgical management are based on the gene identification. Specific genes have been identified, each of them are involved in specific aortopathy pathways (Table 3). Multi-gene panel, single-gene testing and genomic sequencing all can be utilized as evaluation strategy to identify the genetic cause of NS-TAD formm.[26] For some genes, specific recommendations exist in order to tailor the most appropriate clinical and/or surgical intervention. In patients with ACTA 2 gene mutations, elective surgical repair is advisable when the diameter of the ascending aorta/aortic root reaches 4.5 cm;[28] for carriers of FBN1 gene mutations, operation should be considered when the diameter of the aneurysm reaches 5 cm;[2] fin cases with TGFBR1/TGFRB2 mutations surgical management should be anticipated when the aortic root diameter reaches 4.0 cm.[29]

Table 4. Characteristics of imaging modalities for TAD assessment (adapted from Evagelista A.)[27]				
Variable	**TTE**	**TOE**	**CTA**	**MRA**
Readily available	+++	+	+++	+
Quickly performed	+++	++	++	+
Non-invasive	+++	+	+++	+++
No iodinated contrast	+++	+++	-	+++
No radiation	+++	+++	-	+++
Dynamic and functional information	++	++	-	+++
Aortic wall visualization	+	++	+++	+++
Assessment of aortic root/ascending aorta	++	++	+++	+++
Assessment of aortic arch and carotid vessels	-	+	+++	+++
Assessment of descending aorta	-	++	+++	+++
Assessment of aortic valve	+++	+++	-	++
Assessment of left ventricle function	+++	+++	-	-
3D multiplanar and high resolution	-	-	+++	+++
Measurement accuracy	+	+	+++	++
Costs	+++	+++	+	-
Abbreviations: + limited; ++ good; +++ excellent; - bad. CTA, CT angiography, MRA, MR angiography				

3.3.5. The knowledge gap

The 2014 European Society of Cardiology (ESC) Guidelines for the management of NS-TAD include a level I recommendation for the screening of first-degree relatives of patients with TAA and /or TADA to identify those with asymptomatic disease, and for referring the patient to a geneticist for family investigation, once a familial NS-TAD from is recognized.[1] However, the evidence to support these recommendation is level C, based on the consensus of opinion of the experts, small and retrospective studies. Similarly, the American Heart Association (AHA) 2010 guidelines on screening for NS-TAD primarily consist of recommendations based on level C evidence.[2] This contrasts with the evidence-based for the screening modalities of other syndromic TAD conditions. In addition, screening of second-degree relatives of patients affected by NS-TAD and screening of other arterial district are not well established, presenting both a level IIa recommendation only.[1,2] In addition, no data about the effectiveness or cost-effectiveness of a screening program in relatives of NS-TAD patients are present, and indications for genetic analysis are not well established as well the preferred TAD imaging modality.[1,2]

3.3.6. Why it is important to do this review

Compared to syndromic TAD forms (i.e. Marfan or Loeys-Dietz syndromes) which are characterized by relevant physical features, therefore alerting clinicians to the underlying aortopathy, non-syndromic (NS) TAD forms lack of clear external physical signs, and are characterised by silent aneurysm formation and dissection.[22,24] Thoracic aortic disease (TAD) have high mortality, and early recognition is essential in order to establish a prompt clinical and surgical management,[1,2] therefore identifying as early as possible those who would benefit from prompt treatment and preventive measures.

4. OBJECTIVES

The overarching aim of the present review is to determine the effectiveness of screening of asymptomatic relatives of NS-TAD probands, highlighting the incidence and prevalence of TAD in this population. Secondary objectives will be to catalogue all screening modalities (both genetic and imaging) adopted in the above relatives, and to assess the effectiveness or cost-effectiveness of screening.

4.1. Hypothesis

It is our hypothesis that systematic screening of first- and second-degree relatives of patients affected by NS-TAD will provide a substantial benefit in identifying silent TAD and preventing related death.

Furthermore systematic review of the existing evidence may help with clarifying the best cost-effective screening modality or combination of modalities (genetic vs imaging) and/or imaging tools (TTE vs CT vs MRI), and may contribute to create a catalogue with all the known genetic markers associated with TAD.

4.2. Aims

The aims of the present review will be:

1. To summarise published studies that have considered the screening in relatives of patients with by NS-TAD;
2. To estimate the incidence and prevalence of TAD in family members of patients with NS-TAD of silent and undiagnosed disease of thoracic aorta (TAA and TADA);
3. To provide a defined screening strategy to identify potential individuals affected by TAD who will benefit the most from tailored clinical or surgical managements;
4. To provide a comprehensive list of genes, which can be utilized as risk assessment in family members of a proband with NS-TAD.

5. METHODS

5.1. Criteria for Selecting Studies

5.1.1. Types of studies

We will consider clinical studies that have performed genetic and/or imaging evaluation of relatives of patients affected by NS-TAD. The following types of studies will be analysed:

1. Clinical randomised trials;
2. Controlled before-and-after studies;
3. Prospective and retrospective cohort studies;
4. Cross-sectional studies;
5. Case-control studies;
6. Case series.

Study design features will be assessed according to established criteria from the Cochrane Handbook.[30] In addition, inclusion and exclusion criteria for qualitative and quantitative analyses will be presented according to PICOS criteria.

5.1.2. Study exclusion criteria

Exclusion criteria will include:

1. Studies where screening is based on clinical patient evaluation only;
2. Studies where screening does not include genetic patient evaluation and/or patients are not subjected to recognised imaging modality such as TTE/TOE, CT and MRI of the thoracic aorta;
3. Studies where screening is not based on prospective recruitment/analysis of the proband relatives;
4. Studies where screening involved patients without clear differentiation from syndromic forms;
5. Repeat publications of the same analysis or dataset;
6. Conference abstracts;
7. Editorials & opinion pieces;
8. Books or grey literature.

5.1.3. Types of participants

Relatives of probands with a diagnosis of NS-TAD, including aneurysm, aortic rupture, acute/chronic aortic dissection, intramural hematoma, and penetrating ulcer of the thoracic aorta.

5.1.4. Variable definitions

- Familial non-syndromic TAD will be defined as those occurring in patients having 1 or more first-generation relatives with an aortic aneurysm and no history of MFS or any other connective tissue disease (Table 2).[22]
- Sporadic TAD will be defined as those occurring in patients apparently without another relative with TAD.
- Patients affected by TAD will be considered in the entire family pedigree, and will be defined as those individuals having a diagnosis of TAD. Their percentage will be considered in the obtained family pedigree.

- Diagnosis of TAD (phenotype) will be considered if confirmed by imaging (TTE and/or CT and/or MRI), post-mortem examination or intraoperative findings. Sudden deaths will be excluded from TAD diagnosis.
- Percentage (%) of observed TAD will be calculated from the total number of relatives in the entire pedigree.
- Patients defined as eligible for screening (genetic and/or imaging) will include first- and second-degree relatives of a proband with NS-TAD; spouse and deceased patients will be included if blood/tissue samples were available for analysis.
- Patients screened will be defined as those having had prospective genetic screening and imaging studies (TTE and/or CT and/or MRI). Patient deceased will be included in the "patient screened category" if they had blood or tissue collected at the time of operation , which allowed for subsequent genetic analysis.
- Percentage (%) of screened patients will be calculated from the number of patients considered eligible for screening.
- Proband (index patient) will be defined as the first family member affected by NS-TAD. It will be denoted as shaded square (male) or circle (female) in the family pedigree marked by an arrow.
- Penetrance (%) will be defined as: $\frac{\text{n. of patients affected by TAD positive for the gene mutation}}{\text{Subjects with positive gene mutation}}$
- First-degree relatives (FDR) of the proband will include:
    1) Parents (father and mother)
    2) Child (daughter and son)
    3) Siblings (brother and sister).
- Second-degree relatives (SDR) will include:
    1) Grandparent
    2) Grandchild
    3) Aunt and uncle
    4) Nephew and niece.
- Third degree relatives (TDR) will include:
    1) Great-grandparent
    2) Great-grandchild
    3) Cousin.
- Thoracic aortic dissection (TADA) category will include type A and B acute or chronic forms as well as other acute aortic syndromes (rupture, intramural hematoma, penetrating ulcer).

5.1.5. Exposures of Interest

The primary exposure of interest will be a disease of the thoracic aorta (aneurysm and dissection).

5.1.6. Types of outcome measures

• The primary outcome will be new diagnosis of TAD, including aneurysms or dissections, in relatives of patients with NS-TAD forms.

• Secondary outcome will include:

a. Gender TAD preponderance;
b. Rate between TAA and TADA in the NS-TAD form;
c. Age at diagnosis of TADA;
d. Concomitant vascular/cardiac associated diseases;
e. Concomitant associated clinical features;
f. Genetic risk assessment with the penetrance of the NS-TAD form;
g. Cost-effectiveness of adopted imaging modality.

5.2. Search Methods for Identification of Studies

5.2.1. Search strategy

We will search the following databases (from inception to 31 December 2017):

1. Cochrane Library
2. PubMed/MEDLINE (1946 to 31 December 2017);
3. Embase (1974 to 31 December 2017);

No language restriction will be applied. We also anticipate that articles not in English will be translated using Google Translate® which is a free, Web-based program with a reputation for accurate, natural translation.[31,32]

5.2.2. Searching other resources

A systematic search in the Online Mendelian Inheritance in Man (OMIM) database (http://www.omim.org/) will be also performed through December 2017, using similar terms of the below literature search.
Finally, we will check references of all identified studies, relevant review articles, and current treatment guidelines for further literature. These searches will be limited to the 'first generation' reference lists.

5.2.3. Results of the scoping search

A preliminary scoping search (PUBMED) using the terms (aorta, thoracic) or (aortic aneurysm) or (aortic dissection) AND (relatives) or (pedigree) or (siblings) and (screening) and (humans) accounted for 1,022 sources.

5.3. Data collection

5.3.1. Selection of studies (screening-eligibility-inclusion)

Two authors (G.M. and D.R.) will screen all titles and abstracts of papers identified for relevance to the review aims (electronic search). An independent search with the review of all articles will be conducted by a third review (G.J.M.). Studies clearly not meeting the eligibility criteria will be excluded at this stage. Remaining studies will be assessed on the basis of their full text for inclusion or exclusion using the criteria indicated above. At this stage, two reviewers (G.M. and D.R.) will independently assess eligibility. Disagreements will be resolved by consensus in discussion with a third reviewer (G.J.M.). Numbers of studies assessed, included and excluded will be recorded. Duplicate reporting of studies will be carefully assessed and indicated.

5.3.2. Qualitative analysis

Two investigators independently will appraise all articles that will met inclusion criteria, and study quality will be assessed using the Newcastle-Ottawa Scale, and the U.S. Preventive Services Task Force (USPSTF).[33,34] Methdodological quality will be also assessed considering the Cochrane Risk of Bias toll.[35]
Disagreement about critical appraisal will be resolved by discussion. The qualitative analysis will help to explore questions such as how patient selection, treatment and type of study may have influenced the primary effect estimate. In addition, the following questions will be considered for a qualitative analysis:

1. Was the study population well described?
2. Were the outcomes of interest clearly defined?
3. Were the exposures of interest (primary and secondary) well defined?
4. Does the article state both inclusion and exclusion criteria?
5. Were the analysed variables clearly defined?
6. Was the screening prospectively conducted?
7. Were relatives prospectively invited and subject to screening (genetic and/or imaging)?

5.3.3. Data extraction and management

Two authors (G.M. and D.R.) will extract selected data from eligible studies, which will be subsequently checked by a third author (G.J.M.). The following data will be collected and tabulated with Microsoft Excel (Microsoft Corporation, Redmond, WA):

1. Study characteristics:

Author/authors; date of publication; country of origin including the university where the study was mainly carried out; inclusion/exclusion criteria.

2. Population characteristics:

Ethnic origin of the patient population; number of family enrolled in the screening program; identification of the family; number of subjects in the family pedigree; number of eligible individuals for screening purpose; number of screened relatives.

3. Exposures:

Rate of newly diagnosed relatives with TAD and/or TADA

4. Outcomes:

Rate of registered sudden death; age (years) at diagnosis for patients with TADA (mean and range); gender preponderance; rate and type of concomitant associated cardiac or vascular diseases; rate and type of concomitant associated clinical features; penetrance; identification of genetic mutation.

5. Screening modality:

Type of adopted genetic screening; type of imaging modality adopted for screened.

Two authors (G.M. and R.D.) will perform data extraction independently. Data will be extracted onto study specific data extraction form. Disagreements will be resolved by consensus between the authors or by discussion with a third author where necessary (G.J.M.). A second check of all data entry will be performed in order to avoid discrepancies. Missing data will be requested from study authors. If data are unclear, missing, or presented in a form that is unable to be reliably extracted, authors will be contacted to assist in the process. The corresponding author will be initially contacted by email, with the first author (if not the corresponding author) copied into all correspondence. If email addresses are not available, authors will be contacted by phone. Authors will be given seven days to respond to emails, after which they will be followed up with a phone call and an additional email. If no responses are received after an additional seven days, another phone call will be made to contact the author. Other attempt will occur for other seven days; thereafter the authors will be classified as uncontactable.

5.5. Measures of treatment effect and data analysis

5.5.1. Measures and data representation

A narrative synthesis of the included studies will be provided, focusing on the effectiveness of genetic and/or imaging in the new diagnosis of TAD, including aneurysms or dissections, in relatives of patients with NS-TAD forms. Detailed tables of the findings from the included studies will be provided, with reference to the type of study (i.e. randomized, cohort studies, case control studies...), origin (country), the study period (year), the inclusion/exclusion criteria, type of analysed outcomes, and modality of screening adopted. In addition, additional tables will be provided listing relevant characteristics of each study.

5.5.2. Data analysis

All extracted data will be tabulated with Microsoft with Microsoft Excel (Microsoft Corporation, Redmond, WA). Percentage for screened, eligible patients as well subjects affected by TAA and/or TADA will be provided. Percentages of other associated concomitant vascular and cardiac disease will be listed as well concomitant associated clinical features.

6. COMPETING INTERESTS

The authors declare that they have no competing interests.

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SUPPLEMENTAL METHODS

Literature search strategy

Our keywords and MeSH terms pertinent to the exposure of interest were used in relevant combinations and they are showed below.

PubMed	
Website	https://www.ncbi.nlm.nih.gov/pubmed
Access	December, 31 2017
Filters	none
Fields	Title, Abstract
Search terms	“aorta, thoracic”
	“aortic aneurysm“
	“aortic dissection“
	“aneurysm“
	“dissecting“
	“familial aortic aneurysm”
	“sporadic thoracic aorta”
	“screening”
	“screening aortic aneurysm”
	“screening
	“first-degree relatives”
	“relatives”
	“siblings”
	“pedigree”
	"echocardiography"
	"computed tomography"
	"magnetic resonance"
	“gene”
	“genetic”
	“linkage analysis”
	“next-generation sequencing”
	“mutation”
	“whole exome”
	“exome sequencing”
	“exome sequence”
	“targeted array”
	“genome-wide association study”
	“whole genome sequencing”
	“whole genome sequence”
Number of articles	**10364** (10094 + 270)
Search	10094

("aorta, thoracic" OR "aortic aneurysm" OR "aortic dissection" OR "aneurysm" OR "dissecting") AND ("screening" OR “screening aortic aneurysm”) AND ("echocardiography" OR "computed tomography" OR "magnetic resonance" OR “next-generation sequencing” OR “next-generation sequence” OR “genetic” OR “genes” OR “gene” OR “mutation” OR “whole-exome” OR “whole exome” OR “exome sequencing” OR “exome sequence” OR “targeted array” OR “genome-wide association study” OR “whole genome sequencing” OR “whole genome sequence” OR “linkage analysis”)

Search 270
("aorta, thoracic" OR "aortic aneurysm" OR "aortic dissection" OR "aneurysm" OR "dissecting") AND ("screening" OR “screening aortic aneurysm”) AND ("relatives" OR "siblings" OR "pedigree" OR "first degree relatives")

EMBASE

Website	https://hdas.nice.org.uk/
Access	December, 31 2017
Filters	none
Fields	Title, Abstract
Search terms	“thor*”
	“aortic aneurysm“
	“aortic dissection“
	“aneurysm“
	“dissecting“
	“familial aortic aneurysm”
	“sporadic thoracic aorta”
	“screening”
	“screening aortic aneurysm”
	“screening
	“first-degree relatives”
	“relatives”
	“siblings”
	“pedigree”
	"echocardiography"
	"computed tomography"
	"magnetic resonance"
	“gene”
	“genetic”
	“linkage analysis”
	“next-generation sequencing”
	“mutation”
	“whole exome”
	“exome sequencing”
	“exome sequence”
	“targeted array”
	“genome-wide association study”
	“whole genome sequencing”
	“whole genome sequence”

Search **914**
((((("aorta" AND "thor*") OR "aortic aneurysm" OR "aortic dissection" OR "aneurysm" OR "dissecting") AND ("screening" OR "screening aortic aneurysm")) AND ("echocardiography" OR "computed tomography" OR "magnetic resonance" OR "next-generation sequencing" OR "next-generation sequence" OR "genetic" OR "genes" OR "gene" OR "mutation" OR "whole-exome" OR "whole exome" OR "exome sequencing" OR "exome sequence" OR "targeted array" OR "genome-wide association study" OR "whole genome sequencing" OR "whole genome sequence" OR "linkage analysis")).ti,ab

Cochrane Library

Website	http://onlinelibrary.wiley.com/cochranelibrary/search
Access	December, 31 2017
Filters	none
Search option	Search Manager
Search terms	“thoracic aorta” “thoracic aortic aneurysm” “thoracic aortic dissection” "familial aortic dissection" “screening “ “first-degree relatives” “siblings” “pedigree” “echocardiography” “computed tomography” “magnetic resonance” “gene” “genetic” “linkage analysis” “mutation” “exome sequencing” “exome sequence” “genome-wide association scan” "genome wide linkage scan" “whole genome sequencing” “whole genome sequence”
Number of articles	**165** (13 + 124 + 24 + 4)

Search 13
("thoracic aorta" OR "thoracic aortic aneurysm" OR "thoracic aortic dissection" OR “familial aortic dissection”) AND ("screening") AND ("first degree relatives" OR "family" OR “pedigree” OR "echocardiography" OR "computed tomography" OR "magnetic resonance" OR "gene" OR “genetic” OR “linkage analysis” OR “mutation” OR “exome sequencing” OR “exome sequence” OR “genome-wide association scan” OR "genome wide linkage scan" OR “whole genome sequencing” OR “whole genome sequence”)

Search 124
("thoracic aorta" OR "thoracic aortic aneurysm" OR "thoracic aortic dissection" OR “familial aortic dissection”) AND ("echocardiography" OR "computed tomography" OR "magnetic resonance" OR "gene" OR “genetic” OR “linkage analysis” OR “mutation” OR “exome sequencing” OR “exome sequence” OR “genome-wide association scan” OR "genome wide linkage scan" OR “whole genome sequencing” OR “whole genome sequence”)

Search 24
("thoracic aorta" OR "thoracic aortic aneurysm" OR "thoracic aortic dissection" OR “familial aortic dissection”) AND ("screening")

Search 4
("thoracic aorta" OR "thoracic aortic aneurysm" OR "thoracic aortic dissection" OR “familial aortic dissection”) AND ("screening") AND ("first degree relatives" OR "family" OR “pedigree”)

OMIM

Website	https://www.omim.org
Access	December, 31 2017
Filters	Title

Entries	2454	for	“thoracic aneurysm-associated genes”
Entries	582	for	“aortic aneurysm, familial thoracic”
Entries	59	for	“thoracic aneurysm/dissection”
Entries, total	3095		
Papers identified	**106**		

Citations identified through “first-generation” reference list

Study (Author/Year)	Ref.N.
Barbier et al. 2014[1]	38
Bee et al. 2012[2]	26
Chamney et al. 2015[3]	9
Disabella et al. 2011[4]	19
Disertori et al. 1991[5]	21
Dong et al. 2014[6]	12
Francke et al. 1995[7]	33
Gago-Diaz et al. 2014[8]	24
Gago-Diaz et al. 2016[9]	13
Guo et al. 2001[10]	28
Guo et al. 2007[11]	30
Guo et al. 2009[12]	33
Guo et al. 2011[13]	20
Guo et al. 2013[14]	21
Guo et al. 2015[15]	40
Guo et al. 2016[16]	27
Hannuksela et al. 2015[17]	14
Hannuksela et al. 2016[18]	29
Harakalova et al. 2013[19]	23
Hasham et al. 2003[20]	26
Kakko et al. 2003[21]	20
Kent et al. 2013[22]	23
Keramati et al. 2010[23]	22
Khau Van Kien et al. 2004[24]	37
Khau Van Kien et al. 2005[25]	33
Kuang et al. 2016[26]	40
Loscalzo et al. 2007[27]	46
Marwick et al. 1987[28]	7
McManus et al. 1987[29]	45
Milewicz et al. 1998[30]	16
Morisaki et al. 2009[31]	21
Pannu et al. 2005[32]	31
Pannu et al. 2007[33]	38
Regalado et al. 2011[34]	23
Regalado et al. 2011[35]	23

Regalado et al. 2011[36]	27
Renard et al. 2013[37]	35
Robertson et al. 2016[38]	36
Sherrah et al. 2016[39]	30
Takeda et al. 2015[40]	9
Teixidó-Turà et al. 2014[41]	6
Tortora et al.[42]	24
Tran-Fadulo et al. 2006[43]	21
Tran-Fadulo et al. 2009[44]	21
Vaughan et al. 2001[45]	35
Wang et al. 2010[46]	29
Wang et al. 2013[47]	35
Ware et al. 2014[48]	19
Warnes et al. 1985[49]	12
Weigang et al. 2007[50]	30
Yoo et al. 2010[51]	15
Zhu et al. 2006[52]	30
Ziganshin et al. 2015[53]	23
Total	**1348**

Table S1. PRISMA checklist of items to include when Reporting a Systematic Review or Meta-analysis*

Section/topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4 (Data S1)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4 (Data S1)
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4 (Data S1)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4,5 (Data S1)
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4,5 (Data S1)
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4,5 (Table S2)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6

			(Table S9)
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-10 (Supplement)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11,12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

*From: Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

Table S2. PICOS criteria for inclusion and exclusion of studies into meta-analysis

Parameter	Inclusion criteria	Exclusion criteria
Patients	Patients affected by NS-TAD	Patients affected by syndromic TAD and other cardiac diseases other than TAD
Intervention	Screening using the genetic and/or imaging modalities, including transthoracic echocardiography, computed tomography, and magnetic resonance	-
Comparator	The screening interventions listed above versus each other or versus no intervention	-
Outcomes	Primary: new diagnosis of TAD (aortic aneurysm and dissection) in first-, second-, and third-degree relatives Secondary: effectives of screening modality (eligible vs screened relatives), disease-specific mortality, disease specific genetic mutation, cost-effectiveness, age and aortic diamters at dissection/grow rate	-
Study design	Clinical randomised trials Controlled before-and-after studies Prospective and retrospective cohort studies Cross-sectional studies Case-control studies	Repeat publications of the same analysis or dataset Conference abstracts Editorials & opinion pieces Books or grey literature

NS indicates non syndromic; TAD, thoracic aortic disease.

Table S3. Full details of the screened family relatives with number and ID of the included families

Study (Author/Year)	Country	NS-TAD Form	Ethnicity	Exclusion criteria	N. Families screened	N. Relatives (pedigree)	Name (ID) of families screened*
Barbier et al. 2014[1]	France	FTAAD	White European (French)	MFS and other syndromic forms of TAAD	2	40	TAA-9801, TAA-9178
Bee et al. 2012[2]	USA	FTAA	White American (80%)	MFS, LDS, and EDS	9	54	ANS, JNW, SY92, JNE, ANHH, ANO, KNA, ANV, KNK
Chamney et al. 2015[3]	United Kingdom	FTAAD	White European (North Irish)	Ns	1	14	ns
Disabella et al. 2011[4]	Italy	FTAAD	ns	MFS, LDS, EDS, BAV, and known mutations in: FBN1, TGFBR1, TGFBR2, NOTCH1, COL3A1	5	37	ns
Disertori et al. 1991[5]	Italy	FTAAD	White European (Italian)	ns	1	30	ns
Dong et al. 2014[6]	China	FTAAD	Chinese (Han)	ns	1	64	ns
Francke et al. 1995[7]	USA	FTAAD	Americans of European descent	ns	1	26	ns
Gago-Diaz et al. 2014[8]	Spain	FTAAD	White European (Spanish)	ns	1	31	ns
Gago-Diaz et al. 2016[9]	Spain	FTAAD	White European (Spanish)	ns	1	30	ns
Guo et al. 2001[10]	USA†	FTAAD	Caucasian (13 pedigrees), Iranian (one pedigree), Japanese (one pedigree)	Excluded linkage to FBN1	15	219	**TAA001, TAA002, TAA003, TAA005**, TAA009, TAA010, TAA011, TAA012, TAA013, TAA014, TAA015, TAA025, TAA030, TAA033, TAA034
Guo et al. 2007[11]	USA†	FTAAD	ns	ns	14	212	TAA015, **TAA020, TAA039, TAA041, TAA105, TAA133**, TAA166, **TAA174, TAA313, TAA327, TAA349, TAA370, TAA377, TAA390**

Table S3 (Continued)

Study (Author/Year)	Country	NS-TAD Form	Ethnicity	Exclusion criteria	N. Families screened	N. Relatives (pedigree)	Name (ID) of families screened*
Guo et al. 2009[12]	USA†	FTAAD	ns	Known genetic syndrome	20	269	**TAA020, TAA039, TAA041, TAA105, TAA133, TAA174,** TAA252, **TAA313, TAA327, TAA331, TAA349, TAA370, TAA377, TAA390,** TAA441, TAA455, p.R212Q, p.R212Q, p.R258C, pT326N
Guo et al. 2011[13]	USA†	FTAAD/pAA	Americans of (Northern) European descent	ns	1	28	TAA254
Guo et al. 2013[14]	USA†	FTAAD	ns	Mutations in already known genes associated with FTAAD	6	89	TAA165, **TAA216**, TAA292, TAA508, TAA561, TAA690
Guo et al. 2015[15]	USA†	BAV/TAA	ns	ns	1	48	TAA059
Guo et al. 2016[16]	USA†	FTAAD	European-American	ns	6	65	TAA111, TAA271, TAA602, TAA703, TAA-9544, TAA-92291,
Hannuksela et al. 2015[17]	Sweden	FTAAD	White European (Swedish)	ns	7	266	FTAAD1, FTAAD2, FTAAD3, FTAAD4, FTAAD5, FTAAD6, FTAAD7
Hannuksela et al. 2016[18]	Sweden	FTAAD	White European (Swedish)	ns	1	46	ns
Harakalova et al. 2013[19]	Holland	TAAD/PDA	White European (Dutch)	ns	2	75	TAAD01-TAAD02
Hasham et al. 2003[20]	USA†	FTAAD	White European (Swiss-German)	ns	1	69	**TAA035**
Kakko et al. 2003[21]	Finland	FTAAD	White European (Finnish)	Family with <2 TAD affected pts	11	213	1,2,3,4,5,6,7,8,9,10,11
Kent et al. 2013[22]	USA	BAV/TAA	ns	Dysmorphic/connective tissue manifestations	14	129	**A,D**,F,**G**,H,**I,J,K,L,M,Q,R**,S,T
Keramati et al. 2010[23]	USA	FTAAD	Iranian	ns	1	23	ns
Khau Van Kien et al. 2004[24]	France	FTAAD/PDA	White European (French)	ns	1	68	**Bourgogne family**

Table S3 (Continued)

Study (Author/Year)	Country	NS-TAD Form	Ethnicity	Exclusion criteria	N. Families screened	N. Relatives (pedigree)	Name (ID) of families screened*
Khau Van Kien et al. 2005[25]	France	FTAAD/PDA	White European (French)	ns	1	87	**Bourgogne family**
Kuang et al. 2016[26]	USA†	FTAAD	White European	Family with <2 TAD affected pts	2	40	TAA337-MS300
Loscalzo et al. 2007[27]	USA	BAV/TAA	ns	ns	13	194	**A,D,G,I,J,K,L,M,N,O,P,Q,R**
Marwick et al. 1987[28]	Australia	FTADiss	Australian	ns	1	17	ns
McManus et al. 1987[28]	USA	FTADiss	White American	ns	1	19	ns
Milewicz et al. 1998[30]	USA†	FTAAD	ns	MFS	6	123	**TAA001, TAA002, TAA003**, TAA004, **TAA005**, TAA006
Morisaki et al. 2009[31]	Japan	FTAAD	Japanese	ns	3	47	1,2,3
Pannu et al. 2005[32]	USA†	FTAAD	White European (Swiss-German)	MFS	4	235	**TAA035**, TAA067,TAA090, TAA150
Pannu et al. 2007[33]	USA†	FTAAD	ns	ns	2‡	27	TAA027, TAA069
Regalado et al. 2011[34]	USA†	FTAAD/ICA	ns	Family with < 2 TAD affected pts; MFS, and LDS	13§	231	TAA008, TAA059, TAA062, TAA113, TAA175, **TAA258**, TAA287, TAA288, TAA311, TAA395, TAA467, TAA480, **TAA549**
Regalado et al. 2011[35]	USA†	FTAAD/ICA/pAA	ns	Family with <2 TAD affected pts	5	106	TAA071, TA0072, TAA115, TAA365, **TAA549**
Regalado et al. 2011[36]	USA†	FTAAD	ns	Family with <2 TAD affected pts; MFS, and LDS	5‖	29	**TAA258**, TAA321, TAA345, TAA394, TAA748
Renard et al. 2013[37]	Belgium	FTAAD	ns	MFS	8	97	1,2,3,4,5,6,7,8
Robertson et al. 2016[38]	Australia	FTAAD	ns	Syndromic TAD, BAV, vasculitis	270	1267	ns
Sherrah et al. 20016[39]	Australia	FTAAD	ns	Patients < 16 or > 60 yrs	ns	ns	ns
Takeda et al. 2015[40]	Japan	FTAAD	Japanese	ns	1	17	ns
Tortora et al. 2017[41]	Italy	BAV/TAA	Ns	Ns	20	97	ns
Teixidó-Turà et al. 2014[42]	Spain	FTAAD	White European (Spanish)	ns	1	36	ns
Tran-Fadulo et al. 2006[43]	USA†	FTAAD	ns	ns	3	153	TAA105, TAA174, **TAA216**

Table S3 (Continued)

Study (Author/Year)	Country	NS-TAD Form	Ethnicity	Exclusion criteria	N. Families screened	N. Relatives (pedigree)	Name (ID) of families screened*
Tran-Fadulo et al. 2009[44]	USA†	FTAAD	ns	Family with <2 TAD affected pts; MFS, and LDS	4	78	TAA009, TAA023, TAA336, TAA339
Vaughan et al. 2001[45]	USA†	FTAA	Northern European	MFS and EDS	3	67	ANA, ANB, ANF
Wang et al. 2010[46]	USA†	FTADiss	ns	Family with <2 TAD affected pts	2	48	TAA026, TAA400
Wang et al. 2013[47]	China	FTAAD	Chinese (Han)	(MFS included)	1[#]	10	Family 4
Ware et al. 2014[48]	USA	FTAAD	White American	ns	1	7	ns
Warnes et al. 1985[49]	USA	FTAAD	White American	ns	1	6	ns
Weigang et al. 2007[50]	Germany	FTAAD	ns	Syndromic TAD	ns	26	ns
Yoo et al. 2010[51]	Korea	FTAAD	Korean	ns	1	20	ns
Zhu et al. 2006[52]	France	FTAAD/PDA	French and American	ns	2	49	“French” and “American” families
Ziganshin et al. 2015[53,**]	USA	FTAAD	ns	ns	1	27	ns
Ziganshin et al. 2015[53,**]	USA	FTAAD	ns	ns	1	17	ns

BAV indicates bicuspid aortic valve; EDS, Ehlers-Danlos syndrome; FTAA, familial thoracic aortic aneurysm; FTAAD, familial thoracic aortic aneurysm and dissection; FTAD, familial thoracic aortic dissection; ICA, intracranial aneurysm; LSD, Loeys-Dietz syndrome; MFS, Marfan syndrome; ns, not specified; ns, not specified; pAA, peripheral artery aneurysm; PDA, patent ductus arteriosus; TAD, thoracic aortic disease.

*Families analysed multiple studies are underlined in similar colours. †Study performed at University of Texas (USA) only. [‡]96 families considered in total, but data available for 2 (pedigree) families only. [§]48 families considered in total, but data available for 13 (pedigree) families only. [‖]183 families considered in total, but data available for 5 (pedigree) families only. [#]Other 6 families with Marfan syndrome considered, but excluded from the analysis (inclusion criteria as per protocol). [**]Data of two different screened families obtained from the same study (53).

Table S4. Full details of the family pedigree, eligible, screened, and affected patients and relatives

Study (Author/Year)	NS-TAD Form	Family N.	Probands N.	Total. N. subjects from pedigree	Subjects eligible for screening		Subjects screened		Subjects affected (aneurysm+dissection)		Newly diagnosed affected relatives (aneurysm+dissection)	
					N.	%	N.	%	N.	%	N.	%
Barbier et al. 2014[1]	FTAAD	2	2	40	35	88	13	33	9	23	7	18
Bee et al. 2012[2]	FTAA	9	9	54	44	81	32	59	21	39	12	22
Chamney et al. 2015[3]	FTAAD	1	1	14	11	79	6	43	6	43	5	36
Disabella et al. 2011[4]	FTAAD	5	5	37	22	59	29	78	15	41	10	27
Disertori et al. 1991[5]	FTAAD	1	2	30	24	80	14	47	4	13	2	7
Dong et al. 2014[6]	FTAAD	1	1	64	53	83	39	61	9	14	8	13
Francke et al. 1995[7]	FTAAD	1	1	26	22	85	23	88	10	38	9	35
Gago-Diaz et al. 2014[8]	FTAAD	1	1	31	22	71	12	39	7	23	6	19
Gago-Diaz et al. 2016[9]	FTAAD	1	1	30	25	83	14	47	11	37	10	33
Guo et al. 2001[10]	FTAAD	15	n/a	219	141	64	121	55	73	33	n/c	n/c
Guo et al. 2007[11]	FTAAD	14	n/a	212	151	71	130	61	53	25	n/c	n/c
Guo et al. 2009[12]	FTAAD	20	n/a	269	176	65	163	61	66	25	n/c	n/c
Guo et al. 2011[13]	FTAAD/pAA	1	1	28	22	79	18	64	9	32	8	29
Guo et al. 2013[14]	FTAAD	6	6	89	49	55	39	44	37	42	31	35
Guo et al. 2015[15]	BAV/TAA	1	1	48	35	73	34	71	8	17	7	15
Guo et al. 2016[16]	FTAAD	6	6	65	38	58	21	32	21	32	15	23
Hannuksela et al. 2015[17]	FTAAD	7	7	270	135	50	106	40	44	16	37	14
Hannuksela et al. 2016[18]	FTAAD	1	1	46	31	67	19	41	6	13	n/c	n/c
Harakalova et al. 2013[19]	TAAD/PDA	2	2	75	47	63	40	53	15	20	13	17
Hasham et al. 2003[20]	FTAAD	1	1	69	61	88	52	75	17	25	16	23
Kakko et al. 2003[21]	FTAAD	11	n/a	213	150	70	115	54	39	18	n/c	n/c
Kent et al. 2013[22]	BAV/TAA	14	14	129	94	73	93	72	48	37	34	26

Table S4 (Continued)

Study (Author/Year)	NS-TAD Form	Family N.	Probands N.	Total. N. subjects from pedigree	Subjects eligible for screening		Subjects screened		Subjects affected (aneurysm+dissection)		Newly diagnosed affected relatives (aneurysm+dissection)	
					N.	%	N.	%	N.	%	N.	%
Keramati et al. 2010[23]	FTAAD	1	1	23	20	87	15	65	13	57	12	52
Khau Van Kien et al. 2004[24]	FTAAD/PDA	1	1	68	50	74	49	72	8	12	7	10
Khau Van Kien et al. 2005[25]	FTAAD/PDA	1	1	87	73	84	78	90	8	9	7	8
Kuang et al. 2016[26]	FTAAD	2	n/a	40	28	70	16	40	11	28	n/c	n/c
Loscalzo et al. 2007[27]	BAV/TAA	13	13	194	137	71	138	71	57	29	44	23
Marwick et al. 1987[28]	FTADiss	1	1	17	15	88	4	24	2	12	1	6
McManus et al. 1987[29]	FTADiss	1	1	19	11	58	8	42	6	32	5	26
Milewicz et al. 1998[30]	FTAAD	6	6	123	89	72	n/a	n/a	30	24	24	20
Morisaki et al. 2009[31]	FTAAD	3	3	47	30	64	9	19	14	30	11	23
Pannu et al. 2005[32]	FTAAD	4	4	235	179	76	72	31	58	25	54	23
Pannu et al. 2007[33]	FTAAD	2	2	27	24	89	23	85	6	22	4	15
Regalado et al. 2011[34]	FTAAD/ICA	13	13*	231	126	55	12	5	52	23	43	19
Regalado et al. 2011[35]	FTAAD/ICA/pAA	5	n/a	106	71	67	36	34	23	22	n/c	n/c
Regalado et al. 2011[36]	FTAAD	5	5	29	16	55	11	38	15	52	10	34
Renard et al. 2013[37]	FTAAD	8	8	97	67	69	29	30	29	30	21	22
Robertson et al. 2016[38]	FTAAD	270	270	nc	n/c	n/c	n/c	n/c	611	n/a	n/c	n/c
Sherrah et al. 2016[39]	FTAAD	539	n/a	nc	n/c	n/c	n/c	n/c	658	n/a	n/c	n/c
Takeda et al. 2015[40]	FTAAD	1	1	17	12	71	9	53	5	29	4	24
Teixidó-Turà et al. 2014[41]	FTAAD	1	1	36	25	69	10	28	3	8	2	6
Tortora et al. 2017[42]												
Tran-Fadulo et al. 2006[43]	FTAAD	3	3	153	106	69	9	6	21	14	18	12
Tran-Fadulo et al. 2009[44]	FTAAD	4	4†	78	62	79	49	63	29	37	26	33
Vaughan et al. 2001[45]	FTAA	3	3	67	61	91	63	94	30	45	27	40

Table S4 (Continued)

Study (Author/Year)	NS-TAD Form	Family N.	Probands N.	Total. N. subjects from pedigree	Subjects eligible for screening		Subjects screened		Subjects affected (aneurysm+dissection)		Newly diagnosed affected relatives (aneurysm+dissection)	
					N.	%	N.	%	N.	%	N.	%
Wang et al. 2010[46]	FTADiss	2	n/a	48	34	71	21	44	10	21	n/c	n/c
Wang et al. 2013[47]	FTAAD	1	1	10	7	70	8	80	2	20	1	10
Ware et al. 2014[48]	FTAAD	1	2	7	5	71	7	100	2	29	0	0
Warnes et al. 1985[49]	FTAAD	1	2	6	4	67	2	33	2	33	0	0
Weigang et al. 2007[50]	FTAAD	1	n/a	26	23	88	23	88	9	35	n/c	n/c
Yoo et al. 2010[51]	FTAAD	1	1	20	18	90	6	30	5	25	4	20
Zhu et al. 2006[52]	FTAAD/PDA	2	n/a	49	49	100	49	100	8	16	n/c	n/c
Ziganshin et al. 2015[53,‡]	FTAAD	1	1	27	24	89	15	56	4	15	3	11
Ziganshin et al. 2015[53,‡]	FTAAD	1	1	17	8	47	15	59	7	41	6	35

BAV indicates bicuspid aortic valve; FTAA, familial thoracic aortic aneurysm; FTAAD, familial thoracic aortic aneurysm and dissection; FTAD, familial thoracic aortic dissection; ICA, intracranial aneurysm; n/a, not available; n/c, not computable; pAA, peripheral artery aneurysm; PDA, patent ductus arteriosus.

*4 probands not affected by aortic diseases (aortic aneurysm and/or dissections). [†]1 proband not affected by aortic disease (aortic aneurysm and/or dissection). [‡]Data of two different screened families obtained from the same study (53).

Table S5. Full details of the first, second and third degree realatives of evelauated probands

Study (Author/Year)	Newly diagnosed affected relatives (aneurysm+dissection)		FIRST DEGREE RELATIVES			SECOND DEGREE RELATIVES			THIRD DEGREE RELATIVES			Spouse	
	N.	%.	N.	Affected N.	Not Screened*	N.	Affected N.	Not Screened	N.	Affected N.	Not Screened	N.	Screened
Barbier et al. 2014[1]	7	18	14	6	3	14	1	0	0	0	0	10	assessed
Bee et al. 2012[2]	12	22	37	11	9	3	1	0	0	0	0	5	assessed
Chamney et al. 2015[3]	5	36	8	2	2	3	3	0	0	0	0	2	assessed
Disabella et al. 2011[4]	10	27	23	8	4	5	2	2	4	0	0	0	not assessed
Disertori et al. 1991[5]	2	7	13	2	3	15	0	11	0	0	0	0	not assessed
Dong et al. 2014[6]	8	13	5	1	0	9	1	4	30	6	0	19	not sepcified
Francke et al. 1995[7]	9	35	15	8	2	9	1	4	0	0	0	1	not assessed
Gago-Diaz et al. 2014[8]	6	19	3	2	0	10	4	1	13	0	8	4	assessed
Gago-Diaz et al. 2016[9]	10	33	12	6	1	14	4	5	3	0	1	0	not assessed
Guo et al. 2001[10]	n/a	n/a	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	assessed
Guo et al. 2007[11]	n/a	n/a	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	assessed
Guo et al. 2009[12]	n/a	n/a	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	assessed
Guo et al. 2011[13]	8	29	7	2	1	9	4	2	6	2	0	5	assessed
Guo et al. 2013[14]	31	35	40	19	1	18	6	4	12	6	0	13	assessed
Guo et al. 2015[15]	7	15	10	2	1	14	1	8	15	4	0	8	assessed
Guo et al. 2016[16]	15	23	21	3	2	22	6	11	13	6	2	3	assessed
Hannuksela et al. 2015[17]	37	14	60	17	8	89	11	15	55	9	27	59	not assessed
Hannuksela et al. 2016[18]	n/a	n/a	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	270	not assessed
Harakalova et al. 2013[19]	13	17	6	2	0	15	2	4	34	9	19	18	assessed
Hasham et al. 2003[20]	16	23	4	3	0	5	2	1	39	11	3	20	assessed
Kakko et al. 2003[21]	n/a	n/a	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	assessed
Kent et al. 2013[22]	34	26	73	24	17	21	4	12	19	6	8	2	assessed

Table S5 (Continued)

Study (Author/Year)	Newly diagnosed affected relatives (aneurysm+dissection)		FIRST DEGREE RELATIVES			SECOND DEGREE RELATIVES			THIRD DEGREE RELATIVES			Spouse	
	N.	%.	N.	Affected N.	Not Screened*	N.	Affected N.	Not Screened	N.	Affected N.	Not Screened	N.	Screened
Keramati et al. 2010[23]	12	52	10	5	2	8	7	1	0	0	0	4	not assessed
Khau Van Kien et al. 2004[24]	7	10	13	4	2	21	1	2	24	2	7	9	assessed
Khau Van Kien et al. 2005[25]	7	8	13	4	2	26	1	2	38	2	7	9	assessed
Kuang et al. 2016[26]	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	not assessed
Loscalzo et al. 2007[27]	44	23	72	26	7	37	10	10	65	8	27	7	assessed
Marwick et al. 1987[28]	1	6	7	1	2	5	0	0	0	0	0	4	not assessed
McManus et al. 1987[29]	5	26	7	2	1	9	3	1	0	0	0	2	not assessed
Milewicz et al. 1998[30]	24	20	44	15	9	44	8	7	7	1	0	22	not assessed
Morisaki et al. 2009[31]	11	23	10	2	1	6	3	2	27	6	7	1	not assessed
Pannu et al. 2005[32]	54	23	18	9	1	35	12	2	121	33	19	57	not assessed
Pannu et al. 2007[33]	4	15	16	3	2	4	1	0	0	0	0	5	assessed
Regalado et al. 2011[34]	43	19	83	22	19	64	8	33	50	13	5	21	not assessed
Regalado et al. 2011[35]	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	not assessed
Regalado et al. 2011[36]	10	34	18	9	0	6	1	4	0	0	0	0	not assessed
Renard et al. 2013[37]	21	22	34	12	5	30	6	7	7	3	4	16	not assessed
Robertson et al. 2016[38]	341	56	n/c	255	n/c	n/c	48	n/c	n/c	38	n/c	n/c	not assessed
Sherrah et al. 2016[39]	n/a	n/a	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	not assessed
Takeda et al. 2015[40]	4	24	5	2	0	6	2	0	2	0	2	3	assessed
Teixidó-Turà et al. 2014[41]	2	6	8	0	3	5	1	1	15	1	4	n/c	not assessed
Tortora et al. 2017[42]	5	21	77	5	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	not assessed
Tran-Fadulo et al. 2006[43]	18	12	14	6	0	45	6	11	63	6	16	28	not assessed
Tran-Fadulo et al. 2009[44]	26	33	31	13	1	23	9	2	4	4	0	13	assessed

Table S5 (Continued)													
Study (Author/Year)	**Newly diagnosed affected relatives (aneurysm+dissection)**		**FIRST DEGREE RELATIVES**			**SECOND DEGREE RELATIVES**			**THIRD DEGREE RELATIVES**			**Spouse**	
	N.	**%.**	**N.**	**Affected N.**	**Not Screened***	**N.**	**Affected N.**	**Not Screened**	**N.**	**Affected N.**	**Not Screened**	**N.**	**Screened**
Vaughan et al. 2001[45]	27	40	27	17	1	20	9	0	2	1	0	15	assessed
Wang et al. 2010[46]	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	assessed
Wang et al. 2013[47]	1	10	7	1	0	0	0	0	0	0	0	1	not assessed
Ware et al. 2014[48]	0	0	4	0	0	0	0	0	0	0	0	1	not assessed
Warnes et al. 1985[49]	0	0	4	0	0	0	0	0	0	0	0	1	assessed
Weigang et al. 2007[50]	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	assessed
Yoo et al. 2010[51]	4	20	7	3	1	7	1	0	0	0	0	5	not assessed
Zhu et al. 2006[52]	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	n/c	assessed
Ziganshin et al. 2015[53,†]	3	11	7	3	1	11	0	8	2	0	2	6	not assessed
Ziganshin et al. 2015[53,†]	6	35	6	4	1	8	2	5	0	0	0	2	not assessed

n/a indicates not available; n/c, not computable.

*Relatives not screened: not available, deceased or not eligible for screening. †Data of two different screened families obtained from the same study.

Table S6. Full details of the screened families and relatives with reference to additional observed cardiovascular diseases and physical features

Study (Author/Year)	NS-TAD Form	Subjects screened			(Associated) Cardiovascular disease			(Associated) Physical features		
		N.	% (pedigree*)	% (eligible†)	Type	N.	%*	Type	N.	%*
Barbier et al. 2014[1]	FTAAD	13	33	37	Arterial tortuosity, MVP, AF	6	15	Pectus, ARAC, High arched palate	5	13
Bee et al. 2012[2]	FTAA	32	59	73	-	-	-	Pectus, Joint hypermobility	14	26
Chamney et al. 2015[3]	FTAAD	6	43	55	-	-	-	Iris flocculi	4	29
Disabella et al. 2011[4]	FTAAD	19	51	83	ICA, Coronary artery dissection	3	8	IH, varicose vein, Iris flocculi, Iris hypoplasia, Myopia, Cornea plana, Spontaneous pneumothorax, Scoliosis, Joint laxity, Pes planus, Livedo reticularis, Cheloid scars	16	43
Disertori et al. 1991[5]	FTAAD	14	47	58	-	-	-	Joint hyperextensibility	14	47
Dong et al. 2014[6]	FTAAD	39	61	74	AAA	1	2	-	-	-
Francke et al. 1995[7]	FTAAD	23	88	100	MVP, atrial myxoma	2	8	Pectus, Joint hyperextensibility, Myopia, Dental crowding	10	38
Gago-Diaz et al. 2014[8]	FTAAD	12	39	55	BAV	1	3	Joint laxity, Scoliosis, Dolichocephaly	3	10
Gago-Diaz et al. 2016[9]	FTAAD	14	47	56	-	-	-	Pectus, Skin striae, Myopia, Scoliosis, Wrist and thumb sign	7	23
Guo et al. 2001[10]	FTAAD	121	55	86	-	-	-	-	ns	-
Guo et al. 2007[11]	FTAAD	130	61	86	PDA, BAV, ICA	10	5	Livedo reticularis, iris flocculi	41	19
Guo et al. 2009[12]	FTAAD	163	61	93	BAV, CAD, Moyamoya disease	33	12	Livedo reticularis	17	6
Guo et al. 2011[13]	FTAAD/pAA	18	64	82	pAA	3	11	-	-	-
Guo et al. 2013[14]	FTAAD	39	44	80	Coronary artery dissection, CAA, tortuosity of aorta	5	6	-	0	0
Guo et al. 2015[15]	BAV/TAA	34	71	97	BAV	4	8	-	4	0

Table S6 (Continued)

Study (Author/Year)	NS-TAD Form	Subjects screened			(Associated) Cardiovascular disease			(Associated) Physical features		
		N.	% (pedigree*)	% (eligible†)	Type	N.	%*	Type	N.	%*
Guo et al. 2016[16]	FTAAD	21	32	55	AAA, BAV	5	8	Pectus, Palatus, Dolichostenomelia, Joint laxity/hypermobility, Skin striae, Dural ectasia	ns	-
Hannuksela et al. 2015[17]	FTAAD	106	40	79	-	-	-	-	-	-
Hannuksela et al. 2016[18]	FTAAD	19	41	61	ICA	2	4	-	-	-
Harakalova et al. 2013[19]	TAAD/PDA	40	53	85	PDA	5	7	-	0	0
Hasham et al. 2003[20]	FTAAD	52	75	85	BAV, Coarc	1	1	Pectus, ARAC, Palatus	6‡	9
Kakko et al. 2003[21]	FTAAD	115	54	77	AAA	3	1	ns	0	0
Kent et al. 2013[22]	BAV/TAA	93	72	99	BAV, Coarc, UAV, HLHS, ASD, VSD, TGA, PFO, LCA	25	19	-	0	0
Keramati et al. 2010[23]	FTAAD	15	65	75	-	-	-	-	0	0
Khau Van Kien et al. 2004[24]	FTAAD/PDA	49	72	98	PDA, ICA	13	19	-	0	0
Khau Van Kien et al. 2005[25]	FTAAD/PDA	78	84	96	PDA, ICA	13	15	-	0	0
Kuang et al. 2016[26]	FTAAD	16	40	57	-	-	-	ns	0	0
Loscalzo et al. 2007[27]	BAV/TAA	138	71	92	BAV, Coarc, UAV, HLHS, ASD, VSD, TGA, PFO, LCA	33	17	Mild join hyperextensibility	0	0
Marwick et al. 1987[28]	FTADiss	4	24	27	-	-	-	-	-	-
McManus et al. 1987[29]	FTADiss	8	42	73	-	-	-	IH, Scoliosis, Varicose vein	12	63
Milewicz et al. 1998[30]	FTAAD	ns	-	-	AAA, ICA, BAV	7	6	IH, Scoliosis	15	12
Morisaki et al. 2009[31]	FTAAD	9	19	30	ns	-	-	Iris coloboma	47	100
Pannu et al. 2005[32]	FTAAD	72	31	40	AAA, ICA, RAA, Pulmonary AA	8	3	-	-	-
Pannu et al. 2007[33]	FTAAD	23	85	96	PDA	4	15	ns	27	100
Regalado et al. 2011[34]	FTAAD/ICA	12	5	10	AAA, ICA, RAA	34	15	-	-	-
Regalado et al. 2011[35]	FTAAD/ICA/pAA	36	34	51	AAA, ICA, IAA	10	9	Osteoarthritis, Skeletal, Craniofacial, Skin	25	24

Table S6 (Continued)

Study (Author/Year)	NS-TAD Form	Subjects screened			(Associated) Cardiovascular disease			(Associated) Physical features		
		N.	% (pedigree*)	% (eligible†)	Type	N.	%*	Type	N.	%*
Regalado et al. 2011[36]	FTAAD	11	38	69	AAA, IAA	1	3	ARAC, Skin striae, Myopia	6	21
Renard et al. 2013[37]	FTAAD	29	30	43	AAA, PDA, PS	7	7	Skin translucency	3	3
Robertson et al. 2016[38]	FTAAD	581	46	58	-	-	-	-	-	-
Sherrah et al. 2016[39]	FTAAD	119	-	-	-	-	-	-	-	-
Takeda et al. 2015[40]	FTAAD	9	53	75	-	-	-	-	-	-
Teixidó-Turà et al. 2014[41]	FTAAD	10	28	40	-	-	-	-	-	-
Tortora et al. 2017[42]	BAV/TAA	77	-	-	-	-	-	-	-	-
Tran-Fadulo et al. 2006[43]	FTAAD	9	6	8	AAA, ICA, PFO	5	3	-	-	-
Tran-Fadulo et al. 2009[44]	FTAAD	49	63	79	AAA, ICA, HAA	7	9	Skeletal	9	12
Vaughan et al. 2001[45]	FTAA	45	67	74	AAA, LSA	-	-	-	4	6
Wang et al. 2010[46]	FTADiss	21	44	62	-	-	-	-	-	-
Wang et al. 2013[47]	FTAAD	7	70	100	-	-	-	-	-	-
Ware et al. 2014[48]	FTAAD	7	100	100	AAA, ICA	1	100	Mydriasis	2	29
Warnes et al. 1985[49]	FTAAD	2	33	50	-	-	-	-	0	0
Weigang et al. 2007[50]	FTAAD	23	88	100	-	-	-	-	0	0
Yoo et al. 2010[51]	FTAAD	6	30	33	-	-	-	ns	0	0
Zhu et al. 2006[52]	FTAAD/PDA	49	100	100	PDA	3	6	-	-	-
Ziganshin et al. 2015[53,§]	FTAAD	10	37	42	-	-	-	-	-	-
Ziganshin et al. 2015[53, §]	FTAAD	15	29	63	-	-	-	-	-	-

AAA indicates abdominal aorta aneurysm; AF, atrial fibrillation; ARAC, arachnodactyly; ASD, atrial septal defect; BAV, bicuspid aortic valve; CAA, coronary artery aneurysm; CAD, coronary artery disease; Coarc, coarctation; FTAA, familial thoracic aortic aneurysm; FTAAD, familial thoracic aortic aneurysm and dissection; FTAD, familial thoracic aortic dissection; HAA, aneurysm of the hepatic artery; HLHS, hypoplastic left heart syndrome; IAA, aneurysm of the iliac artery; ICA, intracranial aneurysm; IH, inguinal hernia; LCA, left cerebral artery aneurysm; MVP, mitral valve prolapse; ns, not specified (in the study); PA, pulmonary artery; pAA, peripheral artery aneurysm; PDA, patent ductus arteriosus; Pectus, pectus excavatum and/or carinatum; PFO, patent foramen ovale; PS, pulmonary stenosis; RAA, aneurysm of the renal artery; TGA, transposition of the great arteries; UAV, unicommissural aortic valve; VSD, ventricular septal defect.

*Percentage calculated considering the number of relatives in the entire family pedigree (as per protocol). †Percentage considered among eligible relatives for screening (as per protocol). [‡]Only six family relatives were evaluated. [§]Data of two different screened families obtained from the same study.

Table S7. Details of the adopted imaging modalities for the screening of relatives

Study (Author/Year)	NS-Form	Screening Type	Imaging modality of the aorta				
			TTE	CT	MR	Aortic size cut-off (mm)*	Location cut-off
Barbier et al. 2014[1]	FTAAD	GENETIC+IMAGING	yes	no	no	ns	ns
Bee et al. 2012[2]	FTAA	GENETIC	no	no	no	-	-
Chamney et al. 2015[3]	FTAAD	GENETIC+IMAGING	ns	ns	ns	-	-
Disabella et al. 2011[4]	FTAAD	GENETIC+IMAGING	yes	yes	no	Z-score value ≥ 2.5 (nomograms by Roman et al.[54])	AA/SV/STJ/Asc/Arch/Desc/ Abd Aorta
Disertori et al. 1991[5]	FTAAD	IMAGING	yes	no	no	Ns	ns
Dong et al. 2014[6]	FTAAD	GENETIC+IMAGING	yes	yes	no	42 mm (adults); z score>2 (children)	AR
Francke et al. 1995[7]	FTAAD	GENETIC+IMAGING	yes	no	no	Ns	AR
Gago-Diaz et al. 2014[8]	FTAAD	GENETIC	no	no	no	Asc Aorta > 21mm/m^2	Asc
Gago-Diaz et al. 2016[9]	FTAAD	GENETIC	no	no	no	-	-
Guo et al. 2001[10]	FTAAD	GENETIC	no	no	no	SV plotted against nomograms derived from Roman et al.[54]	SV
Guo et al. 2007[11]	FTAAD	GENETIC	no	no	no	-	-
Guo et al. 2009[12]	FTAAD	GENETIC	no	no	no	Z-score value > 2 (nomograms by Roman et al.[54])	Asc, STJ, SV
Guo et al. 2011[13]	FTAAD/pAA	GENETIC	no	no	no	≥ 42 mm	AA/SV/STJ/Asc
Guo et al. 2013[14]	FTAAD	GENETIC	no	no	no	-	-
Guo et al. 2015[15]	BAV/TAA	GENETIC	no	no	no	-	-
Guo et al. 2016[16]	FTAAD	GENETIC	no	no	no	-	-
Hannuksela et al. 2015[17]	FTAAD	GENETIC+IMAGING	yes	no	yes	Z-score >2	SV/Asc
Hannuksela et al. 2016[18]	FTAAD	GENETIC+IMAGING	yes	yes	yes	TTE measures plotted against nomograms derived from Mirea et al.[55]; MRI data against nomograms derived from Davis et al.[56]	TTE-SV and widest level of Asc; MRI - Asc and Desc at the level of pulmonary bifurcation
Harakalova et al. 2013[19]	TAAD/PDA	GENETIC	no	no	no	42	SV/Asc
Hasham et al. 2003[20]	FTAAD	GENETIC+IMAGING	yes	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	AR/SV/SAR

Table S7 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Imaging modality of the aorta				
			TTE	CT	MR	Aortic size cut-off (mm)*	Location cut-off
Kakko et al. 2003[21]	FTAAD	GENETIC+IMAGING	yes	no	no	TTE measures plotted against the nomogram derived from Vasan et al.[57]	AR
Kent et al. 2013[22]	BAV/TAA	GENETIC+IMAGING	yes	no	no	z score ≥ 2 (nomograms of Roman et al.[54])	AR/Asc
Keramati et al. 2010[23]	FTAAD	GENETIC+IMAGING	yes	no	yes[†]	36	AR/SV/SAR
Khau Van Kien et al. 2004[24]	FTAAD/PDA	GENETIC+IMAGING	yes	no	yes	TTE measures plotted against the nomogram derived from Roman et al.[54]	SV/STJ/Asc/HA/Isthmus/Dec
Khau Van Kien et al. 2005[25]	FTAAD/PDA	GENETIC+IMAGING	yes	no	Yes[‡]	TTE measures plotted against the nomogram derived from Vasan et al.[57]	SV/STJ/Asc/HA/Isthmus/Dec
Kuang et al. 2016[26]	FTAAD	GENETIC	no	no	no	-	-
Loscalzo et al. 2007[27]	BAV/TAA	GENETIC+IMAGING	yes	no	no	z score ≥ 2 (nomograms of Roman et al.[54])	AA/AR/STJ/Asc
Marwick et al. 1987[28]	FTADiss	IMAGING	yes	no	no	Ns	ns
McManus et al. 1987[29]	FTADiss	IMAGING	yes	yes	no	Ns	ns
Milewicz et al. 1998[30]	FTAAD	GENETIC+IMAGING	yes	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	ns
Morisaki et al. 2009[31]	FTAAD	GENETIC	no	no	no	-	-
Pannu et al. 2005[32]	FTAAD	GENETIC+IMAGING	yes	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	AR/SV/SAR
Pannu et al. 2007[33]	FTAAD	GENETIC+IMAGING	yes	yes	yes	TTE measures plotted against the nomogram derived from Roman et al.[54]	SV/SAR/Asc
Regalado et al. 2011[34]	FTAAD/ICA	GENETIC	no	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	AA/SV/STJ/Asc
Regalado et al. 2011[35]	FTAAD/ICA/pAA	GENETIC	no	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	AA/SV/STJ/Asc
Regalado et al. 2011[36]	FTAAD	GENETIC	no	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	AA/SV/STJ/Asc
Renard et al. 2013[37]	FTAAD	GENETIC	no	no	no	Z-score >3	SV/Asc
Robertson et al. 2016[38]	FTAAD	IMAGING	yes	yes	yes	Aortic index and Z-score	SV/Asc
Sherrah et al. 20016[39]	FTAAD	IMAGING	yes	yes	yes	TTE measures (z score ≥ 2) plotted against the nomograms from Wolak et al.[58]	SV/Asc
Takeda et al. 2015[40]	FTAAD	GENETIC	no	no	no	-	-

Table S7 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Imaging modality of the aorta				
			TTE	CT	MR	Aortic size cut-off (mm)*	Location cut-off
Teixidó-Turà et al. 2014[41]	FTAAD	GENETIC	no	no	no	-	-
Tortora et al. 2017[42]	BAV/TAA	GENETIC+IMAGING	Yes	no	no	-	-
Tran-Fadulo et al. 2006[43]	FTAAD	GENETIC	no	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	SV/AR/SAR/Asc
Tran-Fadulo et al. 2009[44]	FTAAD	GENETIC	no	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	SV/AR/SAR/Asc
Vaughan et al. 2001[45]	FTAA	GENETIC+IMAGING	yes	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	AA/SV/STJ/Asc/Arch/Desc
Wang et al. 2010[46]	FTADiss	GENETIC	no	no	no	-	-
Wang et al. 2013[47]	FTAAD	GENETIC	no	no	no	-	-
Ware et al. 2014[48]	FTAAD	GENETIC	no	no	no	-	-
Warnes et al. 1985[49]	FTAAD	IMAGING	yes	no	no	Ns	ns
Weigang et al. 2007[50]	FTAAD	GENETIC+IMAGING	yes	yes	yes	Ns	AA/SV/STJ/Asc
Yoo et al. 2010[51]	FTAAD	GENETIC	no	no	no	-	-
Zhu et al. 2006[52]	FTAAD/PDA	GENETIC+IMAGING	yes	no	no	TTE measures plotted against the nomogram derived from Roman et al.[54]	SV/STJ/Asc/HA/Isthmus/Desc
Ziganshin et al. 2015[53]	FTAAD	GENETIC	no	no	no	-	-
Ziganshin et al. 2015[53]	FTAAD	GENETIC	no	no	no	-	-

AA indicates aortic annulus; Abd, abdominal aorta; AR, aortic root; Arch, aortic arch; Asc, ascending thoracic aorta; CT, computed tomography (of the aorta); Desc, descending thoracic aorta; FTAA, familial thoracic aortic aneurysm; FTAAD, familial thoracic aortic aneurysm and dissection; FTAD, familial thoracic aortic dissection; HA, horizontal aorta; ICA, intracranial aneurysm; MR, magnetic resonance(of the aorta); ns, not specified; pAA, peripheral artery aneurysm; PDA, patent ductus arteriosus; SAR, supra-aortic ridge; STJ, sinus tubular junction; SV, sinus of Valsalva; TTE, transthoracic echocardiogram.

*For studies without prospective imaging screening, cut-off aortic size e location of aortic segment provided based on retrospective evaluation of TTE. †Limited number of relatives were subjected to MRI of lumbosacral region. ‡48 subjects undergone cine MR for assessing aortic compliance.

Table S8. Details of the adopted screening modalities in the included studies

Study (Author/Year)	NS-Form	Screening Type	Genetic analysis				
			Techniques used	Gene identified	Genetic mutations	Replicated in an independent cohort	Animal model and/or tissue validation
Barbier et al. 2014[1]	FTAAD	GENETIC+ IMAGING	Whole exome sequencing	MFAP5	c.472C>T (p.Arg158*); c.62G>T (p.Trp21Leu)	Following discover of the MFAP5 mutation in TAA-9801, mutation in MFAP5 were searched in a population of 225 familial and 178 sporadic subjects of French origin and 267 familial subjects of American origin; this led to discover another variant in TAA-9178 co-segregating with TAAD	Effects of mutation were investigated in dermal fibroblasts from affected family members. Mutation led to pure haploinsufficiency of the protein product presumably due to degradation in the endoplasmatic reticulum
Bee et al. 2012[2]	FTAA	GENETIC	Targeted sequencing of ACTA2, MYH11, TGFBR1, and TGFBR2	ACTA2, MYH11, TGFBR2	ACTA2 (p.Gly270Glu, p.Arg118Gln, p.Thr108Met); MYH11 (p.Arg1590Gln, p.Glu1899Asp, intronic 7bp substitution of TGCTTTT>G, 5bp 3' of exon 27); TGFBR2 (p.Ala414Thr, p.His56Asn, p.Asp40Asn)	no	TGFBR2 p.Ala414Thr mutation was shown to have reduced kinase activity in an *in-vitro* gene expression model; TGFBR2 p.His56Asn mutation was associated with delayed downward signalling in a skin fibroblast culture model. Rat myoblasts cells transfected with His56Asn-TGFBR2 or Asp40Asn-TGFBR2 showed reduced downward signalling when stimulated with TGF2
Chamney et al. 2015[3]	FTAAD	GENETIC+ IMAGING	Targeted sequencing	ACTA2	(p.Arg149Cys)	no	no
Disabella et al. 2011[4]	FTAAD	GENETIC+ IMAGING	Targeted sequencing	ACTA2	p.Arg149Cys, p.Asp82Glu, p.Glu243Lys, p.Val45Leu, c.IVS4+1G>A	no	Histological assessment of aortic tissue samples from individuals affected by dissection showed severe medial degeneration, smooth muscle disarray, hyperplasia of the vasa vasorum medial wall smooth muscles

Table S8 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Genetic analysis				
			Techniques used	Gene identified	Genetic mutations	Replicated in an independent cohort	Animal model and/or tissue validation
Disertori et al. 1991[5]	FTAAD	IMAGING	Not performed	n/a	-	-	-
Dong et al. 2014[6]	FTAAD	GENETIC+ IMAGING	Whole exome sequencing - Sanger sequencing	TGFBR1	c.1459C>T (p.Arg487Trp)	no	no
Francke et al. 1995[7]	FTAAD	GENETIC+ IMAGING	Single strand conformation analysis, allele specific oligonucleotide hybridization detection, targeted sequencing	FBN1	c.3379G>A (p.Gly1127Ser)	Attempt of replication in 64 unrelated individuals with MFS, 30 individuals with MFS-related phenotypes and 84 normal controls did not show presence of this mutation	Cultured skin fibroblasts from affected members revealed reduced fibrillin deposition to the control medium
Gago-Diaz et al. 2014[8]	FTAAD	GENETIC	Multiplex ligation dependent probe amplification - Sanger sequencing - Whole exome sequencing	TGFB2	c.1042C>T (p.Arg348Cys)	no	no
Gago-Diaz et al. 2016[9]	FTAAD	GENETIC	Multiplex ligation dependent probe amplification - Massive parallel sequencing - Whole exome sequencing	PRKG1	c.530G>A; (p.Arg177Gln)	no	no
Guo et al. 2001[10]	FTAAD	GENETIC	Genome wide linkage analysis - Targeted sequencing	Locus 5q13-14 D5S806-D5S641	n/a	no	no

Table S8 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Genetic analysis				
			Techniques used	Gene identified	Genetic mutations	Replicated in an independent cohort	Animal model and/or tissue validation
Guo et al. 2007[11]	FTAAD	GENETIC	Genome wide linkage analysis - Targeted sequencing	ACTA2	c.492C>t (p.R149C); c.921A>G (p.R292G); c.397A>C (p.N117T); c.664C>G (p.V154A); c.450T>C (p.Y135H); c.820G>A (p.R258C); c.819C>T (p.R258C); c.400G>A (p.R118Q); c.1105C>A (p.T353N)	The initial discover in TAA327 was followed by ACTA2 sequencing in 97 probands from FTAAD families; this led to detection of 14 further families where ACTA2 mutations co-segregated with TAAD. Other 384 healthy control subjects European descendent served as control	Histological examination of aorta specimens obtained from affected individuals revealed proteoglycan accumulation, elastin fragmentation and areas of increased smooth muscle proliferation in the tunica media of vasa vasorum. Analysis of intracellular actin filaments from mutation carriers showed disturbed actin filament stability
Guo et al. 2009[12]	FTAAD	GENETIC	Exome sequencing - Linkage analysis	ACTA2	n/a	ACTA 2 sequencing in a group of 237 sporadic TAAD patients revealed presence of heterozygous mutations in 6 subjects.	192 matched controls used. Thickening of the walls of aortic vasa vasorum vessels was observed in mutation carriers as compared to control subjects. Smooth muscle cells harvested from mutation carriers showed higher proliferation rate than smooth muscle cells harvested from age and sex matched controls
Guo et al. 2011[13]	FTAAD/pAA	GENETIC	Linkage analysis utilising 50K GeneChips Hind Array by Affymetrix - Candidate gene sequencing	Locus 12q13-14 D12S1691-D12S1726	n/a	no	Medial degeneration observed in the aortic samples from affected individual.
Guo et al. 2013[14]	FTAAD	GENETIC	Whole exome sequencing - Linkage analysis	PRKG1	c.530G>A (p.Arg177Gln)	Initial finding from pedigree TAA216 replicated in pedigrees TAA508, TAA690 and TAA292	Human embryonic kidney cells transfected with the c530G>A PRKG1 gene variant showed much higher enzymatic activity of the gene product when compared to the wild type protein (gain of function mutation)

Table S8 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Genetic analysis				
			Techniques used	Gene identified	Genetic mutations	Replicated in an independent cohort	Animal model and/or tissue validation
Guo et al. 2015[15]	BAV/TAA	GENETIC	Genome wide linkage analysis - Whole exome sequencing	MATA2	c.1031A>C (p.Glu344Ala)	no	447 probands use for comparison. Aortic tissue samples from two affected and mutation positive individuals showed medial degeneration in aortic media (elastin fragmentation and proteoglycan deposition)
Guo et al. 2016[16]	FTAAD	GENETIC	Exome sequencing - Sanger sequencing	LOX	c.839G>T (p.Ser280Arg); c.125G>A (p.Trp42*); c.604G>T (p.Gly202*); c.743C>T (pThr248Ile), c.800A>C (p.Gln267Pro); c1044T>A (p.Ser348Arg)	Exome and Sanger sequencing in an additional 410 unrelated FTAAD probands identified 5 additional rare, disruptive LOX variants	Decreased levels of LOX product's enzymatic activity was confirmed for three missense LOX mutations (p.Thr248Ile, p.Ser280Arg, p.Ser348Arg) in transected HeLa cell culture
Hannuksela et al. 2015[17]	FTAAD	GENETIC+ IMAGING	Targeted analysis of ACTA2, COL3A1, COL5A1, COL5A2, EFEMP2, FBN1, FBN2, GATA5, MYH11, MYLK, NOTCH1, SLCA10, SMAD3, TGFB2, TGFBR1, and TGBFR2	Not identified	-	-	-
Hannuksela et al. 2016[18]	FTAAD	GENETIC+ IMAGING	Whole exome sequencing - Sanger sequencing	MYLK	c3272_3273del (p.Ser1091*)	no	Histopathological assessment of aortic specimens from members of family affected by aortic dissection revealed discontinuation of elastic fibres; no pathological findings were present in histopathological examination of mutation carriers, who underwent prophylactic surgery

Table S8 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Genetic analysis				
			Techniques used	Gene identified	Genetic mutations	Replicated in an independent cohort	Animal model and/or tissue validation
Harakalova et al. 2013[19]	TAAD/PDA	GENETIC	Targeted sequencing, rare copy number variants detection with comparative genome hybridization, detection of intragenic copy number variants performed by analysis of melting curves using qPCR, genome wide linkage analysis	MYH11	MYH11 c.232A>G (p.Lys78Glu), MYH11 c.3766-68delAAG	no	-
Hasham et al. 2003[20]	FTAAD	GENETIC+ IMAGING	Genome-wide linkage analysis - Targeted sequencing of FBLN2	TAAD2	n/a	no	-
Kakko et al. 2003[21]	FTAAD	GENETIC+ IMAGING	Linkage analysis	Locus 5q13-14	n/a	no	-
Kent et al. 2013[22]	BAV/TAA	GENETIC+ IMAGING	Targeted sequencing of NOTCH1	NOTCH1	c.C3269G (p.Thr1090Ser)	no	-
Keramati et al. 2010[23]	FTAAD	GENETIC+ IMAGING	Genome wide linkage analysis - Targeted sequencing of FBN1	Locus 15q21 (FBN1?)	n/a	no	-
Khau Van Kien et al. 2004[24]	FTAAD/PDA	GENETIC+ IMAGING	Linkage analysis - Targeted sequencing of COL3A1. Seven genes and loci tested (COL3A1, FBN1, 3p24-25 or MFS2/TAAD2, 5q13-q14 and 11q23.2-q24, TFAP2B and 12q24)[a]	Not identified	n/a	no	-
Khau Van Kien et al. 2005[25]	FTAAD/PDA	GENETIC+ IMAGING	Whole genome linkage scan - Targeted sequencing	MYH11	n/a	no	-

Table S8 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Genetic analysis				
			Techniques used	Gene identified	Genetic mutations	Replicated in an independent cohort	Animal model and/or tissue validation
Kuang et al. 2016[26]	FTAAD	GENETIC	Exome sequencing	FOXE3	c.457G>C (p.Asp153His)	Exome sequencing was performed in a group of 564 unrelated subjects with FATAAD - 7 other rare variants predicted to disrupt the protein variants were found	Knock-out of FOXE3 in zebrafish leads to disruption of aortic arch development. Knock-out of FOXE3 in mouse embryos leads to reduced cell density in aortic media when compared to wild type
Loscalzo et al. 2007[27]	BAV/TAA	GENETIC+ IMAGING	Targeted sequencing of TGFBR1 and TGFBR2	Not identified	-	-	-
Marwick et al. 1987[28]	FTADiss	IMAGING	Not performed	-	-	-	-
McManus et al. 1987[29]	FTADiss	IMAGING	Not performed	-	-	-	-
Milewicz et al. 1998[30]	FTAAD	GENETIC+ IMAGING	Targeted linkage for FBN1 locus and 3p24-25 locus	No linkage to FBN1 or TAAD2	n/a	no	-
Morisaki et al. 2009[31]	FTAAD	GENETIC	Targeted sequencing of ACTA2	ACTA2	c.445C>T (p.Arg.149Cys); c.616+1G>T (p.Gly152_Thr205 del); c.635G>A (p.Arg212Cys)	no	-
Pannu et al. 2005[32]	FTAAD	GENETIC+ IMAGING	Targeted sequencing of TGFBR2, Targeted linkage analysis	TGFBR2	c.1378C>T (p.Arg460Cys); c.1379G>A (p.Arg460His)	yes	-
Pannu et al. 2007[33]	FTAAD	GENETIC+ IMAGING	Targeted sequencing of MYH11	MYH11	c.3791T > C (p.Leu1264Pro); c.3824G > T p.Arg1275Leu)	yes	Cystic medial degeneration was present in aortic tissue of subject with MYH11 mutations
Regalado et al. 2011[34]	FTAAD/ICA	GENETIC	Targeted sequencing of ACTA2, TGFBR1, and TGFBR2	ACTA2, TGFBR1, TGFBR2	ACTA2 p.Arg258Cys, TGFBR1 p.Arg487Trp, TGFBR2 p.Arg460His,	no	-

Table S8 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Genetic analysis				
			Techniques used	Gene identified	Genetic mutations	Replicated in an independent cohort	Animal model and/or tissue validation
Regalado et al. 2011[35]	FTAAD/ICA/pAA	GENETIC	Whole exome sequencing - Linkage analysis	SMAD3	c.652delA (p.Asn218fs); exone 6 c.836G>A (p.Arg279Lys); exone 6 c.715G>A (p.Glu239Lys); exon 2 c.235C>T (p.Ala112Val)	yes	-
Regalado et al. 2011[36]	FTAAD	GENETIC	Exome sequencing - Sanger sequencing	FBN1	c.7656C>A (p.Cys2552Ter); c.7039_7040delAT (p.Met2347Valfs*19); c.813C>G (p.Cys271Trp); c.6866G>T (p.Cys2289Phe); c.4467T>A (p.Asn1489Lys)	no	-
Renard et al. 2013[37]	FTAAD	GENETIC	Targeted sequencing of ACTA2 and MYH11[†]	ACTA2, MYH11	ACTA2 c.940C>T (p.Arg314X); ACTA2 c.1019_1020delCT(p.Ser340 Cys fs X25); ACTA2 c.124C>A (p.His42Asn); ACTA2 c. 115C>T (p.Arg39Cys); ACTA2 c.145G>A (p.Met49Val), ACTA2 c.112G>A (p.Gly38Arg), ACTA2 c.182A>G (p.Gln61Arg); MYH11 intron 4 IVS32+1G>A	no	Histological examination of tissue samples from patients with ACTA2 and MYH11 mutations revealed medial degeneration. Increased expression of TGFB pathway was observed in individuals with MYH11 mutation
Robertson et al. 2016[38]	FTAAD	IMAGING	Not performed	-	-	-	-
Sherrah et al. 2016[39]	FTAAD	IMAGING	Not performed	-	-	-	-

Table S8 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Genetic analysis				
			Techniques used	Gene identified	Genetic mutations	Replicated in an independent cohort	Animal model and/or tissue validation
Takeda et al. 2015[40]	FTAAD	GENETIC	Targeted sequencing of ACTA2, FBN1, MYH11, SMAD3, TGFB, TGFBR1, and TGFBR2	MYH11	c.3791T>C(p.Leu1264Pro)	no	-
Tortora et al. 2017[42]	BAV/TAA	GENETIC+ IMAGING	Targeted sequencing of ABCC9, ACTA2, CBL, ELN, FBN1, FBN2, MYH11, MYH7, MILK, NOTCH1, TGFB2, TGFB3, TGFBR1 and TGFBR2		n/a	no	-
Teixidó-Turà et al. 2014[42]	FTAAD	GENETIC	ns	ACTA2	c.253G>A (p.Glu85Lys)	no	-
Tran-Fadulo et al. 2006[42]	FTAAD	GENETIC	TaqMan genotyping, Linkage analysis of FBN1, TAAD1, TAAD2, and FAA1 loci, Targeted sequencing of TGFBR2[‡]	Not identified	n/a	no	-
Tran-Fadulo et al. 2009[44]	FTAAD	GENETIC	Targeted sequencing of TGFBR1	TGFBR1	TGFBR1 exon 9 c.1459C>T (p.Arg487WTrp); TGFBR1 exon 9 c.1457T>C (p.Leu486Ser), TGFBR1 exon 5 c.944A>G, p.His315Arg; TGFBR1 exon5 c.934G>A, (p.Gly312Ser)	yes	-
Vaughan et al. 2001[45]	FTAA	GENETIC+ IMAGING	Linkage analysis of known loci (FBN1, FBN2, COL3A1, MFS2, 5q-TAA, FAA1) - Whole genome linkage analysis - Targeted sequencing of SM22α, HSP73	Locus 11q23.3-q24 D11S1341-AFMB031 WC9 (FAA1?)	n/a	no	-

Table S8 (Continued)

Study (Author/Year)	NS-Form	Screening Type	Genetic analysis				
			Techniques used	Gene identified	Genetic mutations	Replicated in an independent cohort	Animal model and/or tissue validation
Wang et al. 2010[46]	FTADiss	GENETIC	Targeted sequencing of CALM1, MYLK, MYL6, MYL6B, and MYL9 - Linkage analysis	MYLK	MYLK c.5275T>C (p.Ser1759Pro), MYLK c.4438C>T (p.Arg1480X)	no	Mutant products of the MYLK gene showed reduced affinity to calmodulin in transfected cells. Mice with tamoxifen-induced smooth muscle cell specific MYLK knock out showed accumulation of proteoglycan in the aortic media
Wang et al. 2013[47]	FTAAD	GENETIC	Targeted sequencing of FBN1, TGFBR1 and TGFBR2	Not identified	n/a	yes	-
Ware et al. 2014[48]	FTAAD	GENETIC	Targeted sequencing of ACTA2, FBN1, MYH11, TGFBR1 and TGFBR2	ACTA2	p.Lys328Asn	no	-
Warnes et al. 1985[49]	FTAAD	IMAGING	Not performed	-	-	-	-
Weigang et al. 2007[50]	FTAAD	GENETIC+ IMAGING	PCR	Not identified	Tested for FBN1, negative	no	-
Yoo et al. 2010[51]	FTAAD	GENETIC	Targeted sequencing of ACTA2, FBN1, and TGFBR2	ACTA2	exone 2 c.76G>T (p.Asp26Tyr)	no	-
Zhu et al. 2006[52]	FTAAD/PDA	GENETIC+ IMAGING	Linkage analysis - Targeted sequencing	MYH11	Substitution at a splice donor site of intron 32 (IVS32+1G→T); c.3810-3881del (p.Arg1241-Leu1264del)	no	Analysis of fibroblast culture obtained from mutation careers showed that transcript of a gene with splice donor site substitution led to production of cDNA without exon 32, which led to deletion of a 71 amino acids in the C-terminal region of the protein; aortic tissue samples from affected members revealed cystic medial degeneration, carriers of the mutation showed reduced aortic compliance
Ziganshin et al. 2015[53]	FTAAD	GENETIC	Whole exome sequencing	MYLK	MYLK p.Ser1759Pro	no	-
Ziganshin et al. 2015[53]	FTAAD	GENETIC	Whole exome sequencing	TGFBR1	TGFBR1 p.Gly188Val	no	-

AD indicates autosomal dominant; FTAA, familial thoracic aortic aneurysm; FTAAD, familial thoracic aortic aneurysm and dissection; FTAD, familial thoracic aortic dissection; GEN, genetic; ICA, intracranial aneurysm; IMAG, imaging; n/a, not available; pAA, peripheral artery aneurysm.

*Seven genes and loci tested (COL3A1, FBN1, 3p24-25 or MFS2/TAAD2, 5q13-q14 and 11q23.2-q24, TFAP2B 12q24): negative correlations. †ACTA2 positive in TAAD isolated; MYH11 positive in family with TAAD and PDA. ‡Relatives from family TAA216 tested for TAAD1, TAAD2, FAA1 and FBN1 with negative correlation, other three relatives from families TAA216, TAA105 and TAA174 tested for TGFBR2 with negative correlation.

Table S9. Quality assessment of the included studies

Study (Author/Year)	Newcastle-Ottawa Scale[58]			Cochrane Risk of Bias Analysis[59]					USPSTF design-specific quality criteria[60]
	Selection	Comparability	Outcome	Selction Bias	Perfomance Bias	Detection Bias	Attrition Bias	Reporting Bias	
Barbier et al. 2014[1]	**	**	*	Low	Low	High	High	High	Fair
Bee et al. 2012[2]	*	**	***	High	High	High	High	High	Fair
Chamney et al. 2015[3]	*	*	**	High	Low	Low	High	High	Poor
Disabella et al. 2011[4]	***	**	***	Low	Low	Low	Low	Low	Fair
Disertori et al. 1991[5]	-	-	*	Unclear	High	Unclear	High	Unclear	Poor
Dong et al. 2014[6]	***	**	***	Low	Low	Low	Low	Low	Fair
Francke et al. 1995[7]	**	*	***	Low	Low	Low	Low	Low	Poor
Gago-Diaz et al. 2014[8]	***	**	***	High	High	Low	High	High	Poor
Gago-Diaz et al. 2016[9]	**	**	**	High	High	Low	High	High	Fair
Guo et al. 2001[10]	*	*	***	High	High	High	Low	Low	Fair
Guo et al. 2007[11]	**	*	***	High	High	Low	Low	Low	Fair
Guo et al. 2009[12]	***	*	***	High	High	High	Low	Low	Fair
Guo et al. 2011[13]	***	*	***	High	High	Low	Low	Low	Fair
Guo et al. 2013[14]	***	*	***	High	High	Low	Low	Low	Fair
Guo et al. 2015[15]	***	*	***	High	High	High	Low	Low	Fair
Guo et al. 2016[16]	***	*	**	High	High	Low	High	High	Fair
Hannuksela et al. 2015[17]	***	*	***	Low	Low	High	High	High	Fair
Hannuksela et al. 2016[18]	***	**	**	Low	Low	Low	High	High	Fair
Harakalova et al. 2013[19]	***	**	***	High	High	Low	High	High	Fair
Hasham et al. 2003[20]	***	**	***	Low	Low	Low	Low	Low	Fair
Kakko et al. 2003[21]	***	**	**	Low	Low	Low	High	High	Poor
Kent et al. 2013[22]	**	**	***	Low	Low	High	High	High	Fair
Keramati et al. 2010[23]	**	*	**	Low	Low	High	High	High	Fair
Khau Van Kien et al. 2004[24]	***	**	***	Low	Low	High	High	High	Poor
Khau Van Kien et al. 2005[25]	***	**	***	Low	Low	High	Low	Low	Fair
Kuang et al. 2016[26]	***	**	*	High	High	Low	High	High	Fair
Loscalzo et al. 2007[27]	***	*	***	Low	Low	High	High	High	Fair
Marwick et al. 1987[28]	-	*	*	Unclear	Unclear	Unclear	Unclear	Unclear	Poor

McManus et al. 1987[29]	-	*	**	Unclear	High	Unclear	Unclear	Unclear	Poor
Milewicz et al. 1998[30]	**	*	**	Low	Low	Low	Low	Low	Fair
Morisaki et al. 2009[31]	**	*	*	High	High	Low	High	High	Fair
Pannu et al. 2005[32]	***	**	*	Low	Low	Low	High	High	Fair
Pannu et al. 2007[33]	***	**	***	Low	Low	Low	Low	Low	Fair
Regalado et al. 2011[34]	**	**	*	High	High	Low	High	High	Fair
Regalado et al. 2011[35]	**	**	**	High	High	High	High	High	Fair
Regalado et al. 2011[36]	**	**	**	High	High	Low	High	High	Fair
Renard et al. 2013[37]	**	**	**	High	High	Low	High	High	Fair
Robertson et al. 2016[38]	***	**	***	Unclear	High	Low	Unclear	Unclear	Good
Sherrah et al. 2016[39]	***	**	***	Unclear	High	High	Unclear	Unclear	Fair
Takeda et al. 2015[40]	**	**	**	High	High	Low	High	High	Fair
Teixidó-Turà et al. 2014[41]	*	*	*	High	High	Low	High	High	Fair
Tortora et al. 2017[42]	*	*	*	Unclear	High	High	High	High	Poor
Tran-Fadulo et al. 2006[42]	**	*	**	High	High	Low	High	High	Fair
Tran-Fadulo et al. 2009[43]	**	**	**	High	High	High	High	High	Fair
Vaughan et al. 2001[44]	***	**	***	Low	Low	High	Low	Low	Fair
Wang et al. 2010[45]	**	*	**	High	High	Low	High	High	Fair
Wang et al. 2013[46]	**	**	**	High	High	High	Low	Low	Fair
Ware et al. 2014[47]	*	*	*	High	High	High	Low	Low	Poor
Warnes et al. 1985[48]	-	*	*	Unclear	Unclear	Unclear	High	High	Poor
Weigang et al. 2007[49]	***	**	**	Low	Low	High	Low	Low	Poor
Yoo et al. 2010[50]	**	**	**	High	High	Low	High	High	Fair
Zhu et al. 2006[51]	***	**	**	Low	Low	High	Low	Low	Poor
Ziganshin et al. 2015[52]	**	*	*	High	High	High	High	High	Poor

USPSTF indicates US Preventive Services Task Force.

Table S10. Genetic architecture of thoracic aortic diseases in non-syndromic forms after screening of the family relatives

Locus	Gene			NS-TAD form	OMIM		Associated TAD	Supporting Reference
	Name	LOCUS OMIM n.	Role		Phenotype	n.		
Known genes								
1q41	TGFB2	Unassigned	TGF-β pathway	FTAAD	LDS type 4	614816	LDS type 4	8
1p33	FOXE3	601094	SMC metabolism	FTAA	AAT11	617349	-	26
2p11.2	MAT2A	Unassigned	SMC metabolism	BAV/TAA	-	Unassigned	-	15
3p24-25	TGFBR2	190182	TGF-β pathway	FTAAD	AAT3	610168	LDS type 2	8,32,34
3q21.1	MYLK	600922	Proteins involved in SMC contraction	FTAAD, FTADiss	AAT7	613780	-	18,47,53
5q23	LOX	Unassigned	ECM proteins	FTAAD	AAT10	617168	-	16
9q22.33	TGFBR1	190181	TGF-β pathway	FTAAD	AAT5	609192	LDS type 1	6,34,44,53
9q34.3	NOTCH1	190198	Neural crest migration	BAV/TAA	AVD1	109730	-	22
10q11.2-q21.1	PRKG1	176894	Proteins involved in SMC contraction	FTAAD	AAT8	615436	-	9,14
10q23.31	ACTA2	102620	Proteins involved in SMC contraction	FTAA, FTAAD	AAT6	611788	-	3,11,12,34,37, 41,48,51
12p13.31	MFAP5	601103	ECM protein	FTAAD	AAT9	616166	-	1
15q21	FBN1	154700	ECM protein	FTAAD	-	154700	MFS	7,23,36
15q22.33	SMAD3	603109	TGF-β pathway	FTAAD/ICA/pAA	-	613795	LDS type 3	34
16p13.12	MYH11	160745	Proteins involved in SMC contraction	FTAAD, FTAAD/PDA	AAT4	132900	-	19,25,33,37,40, 52
Mapped loci without identified gene								
5q13-14	-	-	-	FTAAD	AAT2	607087	-	10
11q23.3-24	-	-	-	FTAA	AAT1	607086	-	45
12q13-14	-	-	-	FTAAD/pAA	-	Unassigned	-	13

AOS indicates osteoarthritis syndrome; AVD, aortic valve disease; BAV, bicuspid aortic valve; ECM, extracellular matrix; FTAA, familial thoracic aortic aneurysm; FTAAD, familial thoracic aortic aneurysm and dissection; FTAD, familial thoracic aortic dissection; ICA, intracranial aneurysm; LDS, Loeys-Dietz syndrome; MFS, Marfan syndrome; pAA, peripheral artery aneurysm; PDA, patent ductus arteriosus; SMC, smooth muscle cell; TGF, transforming growth factor.

Table S11. Current guidelines for diagnosis and treatment of aortic diseases

2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines[62]		
Recommendations	**Class**	**Level of evidence**
Familial thoracic aortic aneurysm and dissections		
Aortic imaging is recommended for first-degree relatives of patients with thoracic aortic aneurysm and/or dissection to identify those with asymptomatic disease.	**I**	**B**
If the mutant gene (FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) associated with aortic aneurysm and/or dissection is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation should undergo aortic imaging.	**I**	**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 imaging of second-degree relatives is reasonable	**IIa**	**B**
Sequencing of the ACTA2 gene is reasonable in patients with a family history of thoracic aortic aneurysms and/or dissections to determine if ACTA2 mutations are responsible for the inherited predisposition	**IIa**	**B**
Sequencing of other genes known to cause familial thoracic aortic aneurysms and/or dissection (TGFBR1, TGFBR2, MYH11) may be considered in patients with a family history and clinical features associated with mutations in these genes	**IIb**	**B**
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	**IIb**	**C**
Bicuspid aortic valve and thoracic aortic disease		
First-degree relatives of patients with a bicuspid aortic valve, premature onset of thoracic aortic disease with minimal risk factors, and/or a familial form of thoracic aortic aneurysm and dissection should be evaluated for the presence of a bicuspid aortic valve and asymptomatic thoracic aortic disease	**I**	**B**
2014 ESC Guidelines[63]		
Familial thoracic aortic aneurysm and dissections		
It is recommended to investigate first-degree relatives (siblings and parents) of a subject with TAAD to identify a familial form in which relatives all have a 50% chance of carrying the family mutation/disease	**I**	**C**
Once a familial form of TAAD is highly suspected, it is recommended to refer the patient to a geneticist for family investigation and molecular testing	**I**	**C**
Variability of age of onset warrants screening every 5 years of 'healthy' at-risk relatives until diagnosis (clinical or molecular) is established or ruled out	**I**	**C**
In familial non-syndromic TAAD, screening for aneurysm should be considered, not only in the thoracic aorta, but also throughout the arterial tree (including cerebral arteries)	**IIa**	**C**
Bicuspid aortic valve and thoracic aortic disease		
Because of familial occurrence, screening of first-degree relatives should be considered	**IIb**	**C**

Figure S1. PRISMA flow diagram of search strategy (through December 31, 2017)

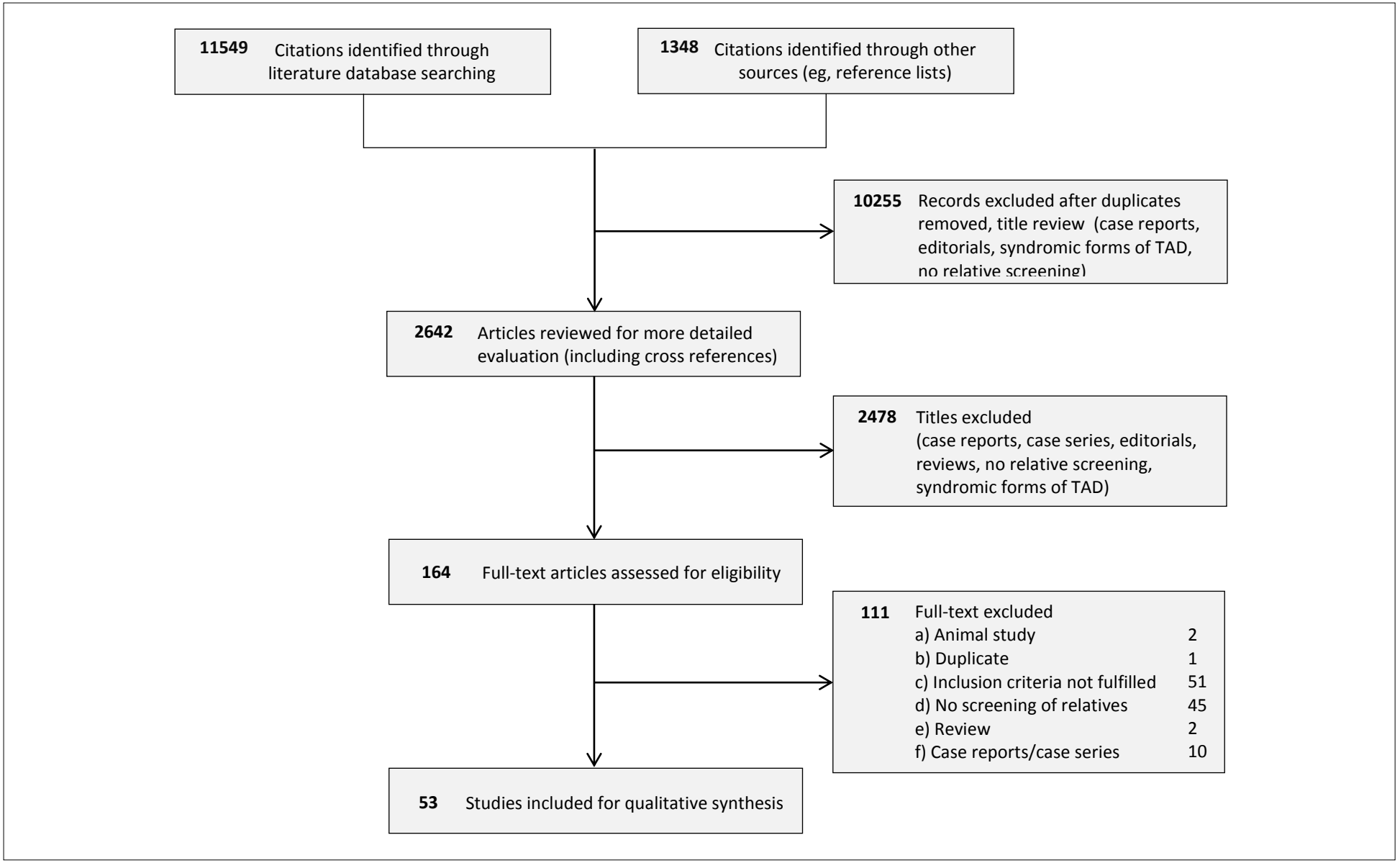
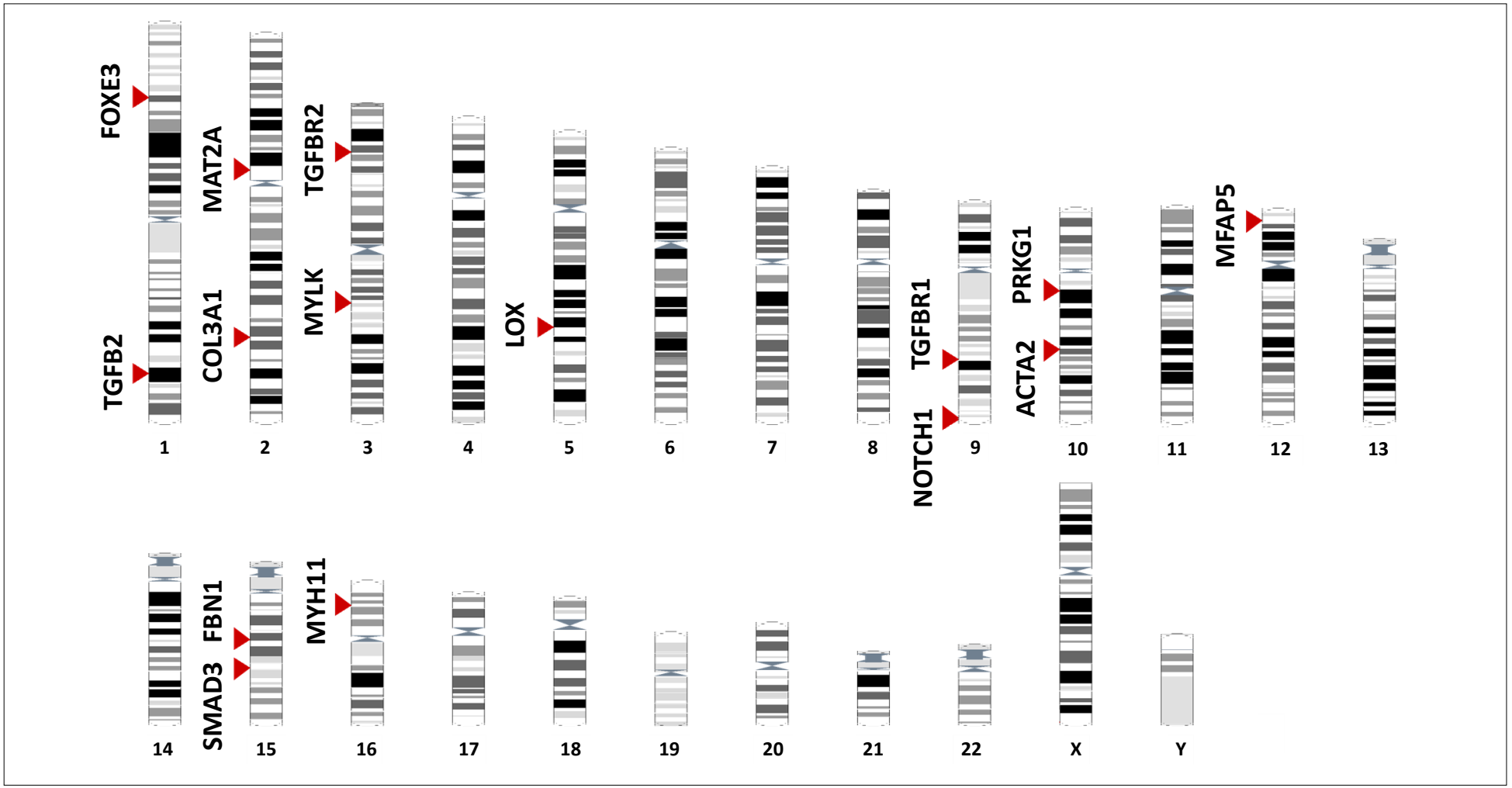


Figure S2. Genes with established causative association with non-syndromic thoracic aortic aneurysms and dissection identified in the present systematic review



ACTA2 = actin alpha 2; COL3A1 = collagen type III alpha 1 chain; FBN1 = fibrillin 1; FOXE3 = Forkhead box E3; LOX = lysyl oxidase; MAT2A = methionine adenosyltransferase 2A; MFAP5 = microfibrillar associated protein 5; MYH11 = myosin heavy chain 11**;** MYLK = myosin light chain kinase; PRKG1 = protein kinase-cGMP-dependent type I; SMAD3 = SMAD family member 3; TGFB2 = Transforming growth factor beta 2; TGFBR1 = transforming growth factor beta receptor 1; TGFBR2 = transforming growth factor beta receptor 2**.**

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