SUPPLEMENTARY DATA

METHODS

DNA isolation and quality analysis

Genomic deoxyribonucleic acid (DNA) was extracted from 4 mL of peripheral blood leukocytes using the Chemagic Prime DNA Blood 4k Kit (Perkin Elmer, United States) following the manufacturer's instructions. The DNA integrity of genomic DNA was checked by regular gel electrophoresis whereas DNA purity (OD260/280 and OD230/260 ratios) was measured using a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, USA). For a more specific and sensitive measurement of DNA concentration, a Quant-iT PicoGreen quantitation assay (Invitrogen, USA) was used.

Aortic diseases gene panel design

A capture panel (Roche, NimbleGen, USA) designed for the routine genetic testing of 1124 genes associated with diverse rare inherited disorders (unpublished data) was used, although only 42 genes (table 1 of the supplementary data) related to different aortic diseases were analyzed in our AAS cohort. The selection of captured genes was based on a comprehensive review of the medical literature, current guidelines for these diseases, and public databases such as Online Mendelian Inheritance in Man (OMIM) and Orphanet. Finally, the input of disease area experts reached a consensus on which genes had sufficient evidence for disease association. The design comprised all exons and the immediate (25bp) flanking regions of each exon. Probes were designed against the human NCBI GRCh37/hg19 reference genome assembly, using the SeqCap EZ application of the NimbleDesign software.

Library preparation and sequence data generation

One microgram of genomic DNA (quantified by PicoGreen) was sheared by mechanical fragmentation using a Covaris S220 instrument (Covaris, USA) to obtain an average fragment size of 180-220 bp (10 % Duty Cycle; Intensity 5; 200 cycles per burst; treatment time 180 s). After DNA size selection using Agencort AMPure XP beads (Beckman Coulter), fragments were end-repaired, A-tailed, and ligated to specific Illumina adapters. Following library normalization, samples were dual indexed (KAPA Dual Indexed Adapter kit), pooled (60 samples in equimolar ratio) and 5 µg of DNA were hybridized to the biotinylated probes for 16-20 hours at 47 °C. Probes-DNA hybrids were recovered and purified using streptavidin-conjugated magnetic beads and PCR amplified. Quantification of libraries was made using Agilent 2100 Bionalyzer (Agilent Technologies, USA) and fluorimetric techniques. Captured libraries, at a concentration of 1.3 pM, were sequenced in multiplexed sequencing runs on the Illumina NextSeq500 sequencer (Illumina, USA) as 150 bp paired-end reads using a NextSeq High-output v2.5 (300 cycles) reagent kit.

Bioinformatic analysis

Burrows-Wheeler Aligner (BWA, version 0.7.12) was used to map sample reads against the hg19 human reference genome. The percentage of reads mapped on-target and the mean coverage in each sample was analyzed with the Capture Assessment Tool (ngsCAT).[1] After duplicate reads removal using the PICARD MarkDuplicates command (version 1.95), the GATK software (version 3.3.0) was used for variant calling and filtering. Reads with coverage < 20 x and strand bias (FS > 60.0) were discarded. SNVs and indels variants were then annotated using ANNOVAR.[2]

Copy-number variations were identified employing the coverage command of BEDtools. In this method, the number of reads for each chromosomal interval of the bed file was normalized using the average number of reads generated per sample. These data were compared with the corresponding data of the other samples in the same sequencing run. A ratio around 1 implied normal dosage;

deletions and duplications ratios were set at < 0.65 and > 1.35 respectively. Deletions and duplications were inspected with the Integrative Genomics Viewer.

Variant prioritization and pathogenicity assessment

Variants were prioritized based on the following: *a)* Allele frequency in the general population (minor allele frequency < 0.01), as reported in freely available repositories of data from large-scale sequencing projects (gnomAD,[3] 1000g,[4] EVS,[5] ExAC[6] and CSVS[7]). *b)* Genomic location in exons or in flanking intronic regions. *c)* Reported in databases of genomic variation as related to human health (ClinVar,[8] HGMD,[9] and LOVD[10]).

Variants meeting these criteria were studied in available family members by Sanger sequencing according to the manufacturer's protocols, using a 3730xl DNA Analyzer (Applied Biosystems, Foster City, CA, USA). Additionally, variants were classified according to their level of pathogenicity based on: *a)* Recommendations of the American College of Medical Genetics and Genomics.[11] *b)* Consistency with clinical suspicion. *c)* Family segregation studies results. *d)* Predicted pathogenicity using Polyphen-2,[12] SIFT[13] and MutationTaster.[14] *e)* Predicted consequences on splicing using Human Splicing Finder.[15] *f)* Experimentally determined functional consequences, when available.

The nomenclature of variants was adjusted to the Human Genome Variation Society guidelines using Mutalyzer.[16]

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Table 1 of the supplementary data. List of analyzed genes and key molecular pathways described for mutated genes in our cohort (*)

Gene name	Gene bank accession	Inheritance	Disease	OMIM (related to aortic disease)	Key molecular pathway
*ACTA2**	NM_001613	AD	Aortic aneurysm, familial thoracic 6	611788	Cytoskeletal/smooth muscle contraction
ADAMTS2	NM_014244	AR	Ehlers-Danlos syndrome, dermatosparaxis type	225410	
ADAMTSL4	NM_019032	AR	Ectopia lentis, isolated, autosomal recessive	225100	
ATP7A	NM_000052	XLR	Ehlers-Danlos syndrome, type9	304150	
B3GAT3	NM_012200	AR	Multiple joint dislocations, short stature, craniofacial dysmorphism, with or without congenital heart defects	245600	
CBS	NM_001178008	AR	Homocystinuria, B6-responsive and nonresponsive types	236200	
CHST14	NM_130468	AR	Ehlers-Danlos syndrome, musculo contractural type1	601776	
*COL1A1**	NM_000088	AD	Ehlers-Danlos syndrome, arthrochalasia type 1	130060	Collagen metabolism
COL1A2	NM_000089	AD	Ehlers-Danlos syndrome, arthrochalasia type 2	617821	
		AR	Ehlers-Danlos syndrome, cardiac valvular type	225320	
COL3A1	NM_000090	AD	Ehlers-Danlos syndrome, vascular type	130050	
		AR	Polymicrogyria with or without vascular type EDS	618343	
COL5A1	NM_001278074	AD	Ehlers-Danlos syndrome, classic type 1	130000	
*COL5A2**	NM_000393	AD	Ehlers-Danlos syndrome, classic type 2	130010	Collagen metabolism
EFEMP2	NM_016938	AR	Cutis laxa, autosomal recessive type IB	614437	
*ELN**	NM_000501	AD	Supravalvar aortic stenosis	185500	
		AD	Cutis laxa, autosomal dominant	123700	ECM matrix
*FBN1**	NM_000138	AD	Marfan síndrome	154700	TGF-b pathway
*FBN2**	NM_001999	AD	Contractural arachnodactyly, congenital	121050	ECM matrix
FKBP14	NM_017946	AR	Ehlers-Danlos syndrome, kyphoscoliotic type 2	614557	
FLNA	NM_001110556	XL	Cardiac valvular dysplasia, X-linked	314400	
		XLD	Heterotopia, periventricular 1	300049	
*GAA**	NM_001079804	AR	Glycogen storage disease 2	232300	Glucose metabolism
GATA5	NM_080473	AD, AR	Congenital heart defects, multiple types 5	617912	
GJA1	NM_000165	AD	Atrio ventricular septal defect 3	600309	
HRAS	NM_001130442	AD	Congenital myopathy with excess of muscle spindles	218040	
KCNJ8	NM_004982	AD	Brugada síndrome	601144	
MED12	NM_005120	XL	Lujan-Fryns síndrome	309520	
MFAP5	NM_003480	AD	Aortic aneurysm, familial thoracic 9	616166	
*MYH11**	NM_001040114	AD	Aortic aneurysm, familial thoracic 4	132900	Cytoskeletal/smooth muscle contraction
*MYLK**	NM_053025	AD	Aortic aneurysm, familial thoracic 7	613780	Cytoskeletal/smooth muscle contraction
*NF1**	NM_000267	AD	Neurofibromatosis	162200	MAPK signaling
NKX2-5	NM_004387	AD	Atrial septal defect 7, with or without AV conduction defects	108900	
*NOTCH1**	NM_017617	AD	Aortic valve disease 1	109730	Developmental
PLOD1	NM_000302	AR	Ehlers-Danlos syndrome, kyphoscoliotic type,1	225400	
PRKG1	NM_006258	AD	Aortic aneurysm, familial thoracic 8	615436	
PTPN11	NM_002834	AD	Noonan syndrome 1	163950	
SKI	NM_003036	AD	Shprintzen-Goldberg syndrome	182212	
*SLC2A10**	NM_030777	AR	Arterial tortuosity syndrome	208050	TGF-b pathway
SMAD3	NM_005902	AD	Loeys-Dietz syndrome 3	613795	

SMAD4	NM_005359	AD	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome	175050	
TGFB2	NM_003238	AD	Loeys-Dietz syndrome 4	614816	
TGFB3	NM_003239	AD	Loeys-Dietz syndrome 5	615582	
*TGFBR1**	NM_004612	AD	Loeys-Dietz syndrome 1	609192	TGF-b pathway
*TGFBR2**	NM_001024847	AD	Loeys-Dietz syndrome 2	610168	TGF-b pathway
ZDHHC9	NM_016032	XL	Mental retardation, X-linked syndromic, Raymond type	300799	

AD, autosomal dominant; AR, autosomal recessive; XL, X-linked; XLR, X-linked recessive; XLD, X-linked dominant.

Table 2 of the supplementary data. Clinical and demographic details for each of the 73 patients under study.

Familiy ID	Genetic classification	Mutated gene	Origin	Stanford classification	DeBakey classification	Clinical presentation	Age (y)	Sex	Type	Risk factors									Clinical symptoms								Aorta diameter (cm)	Treatment criteria	Treatment	Mechanical ventilation	Reintervetion	ICU stay (d)	Hospital stay (d)	Death	Familial screening
										Smoking	Hypertension	Hyperlipidemia	Diabetes mellitus	COPD	Drug abuse	Bicuspic valve	Cardiac surgery	Family history	Pain	Hypertensive crisis	Pulse deficit	Shock	Acute renal failure	Cardiac tamponade	Visceral ischemia	Syncope								
1	Negative	-	Huelva	B	IIIb	Chronic	53	Male	Dissection	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	Yes	No	NA	Conservative	Medical treatment	No	No	4	4	Yes	No
2	Negative	-	Huelva	A	I	Subacute	48	Male	Dissection	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	3	Delayed	Open surgery	Yes	No	8	13	No	No
3	Positive	*MYH11*	Seville	A	I	Acute	49	Male	Dissection	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	No	3.8	Urgent	Open surgery	No	No	7	10	No	No
4	Negative	-	Seville	B	IIIb	Chronic	45	Male	Intramural hematoma	Yes	No	No	No	No	Yes	No	No	No	Yes	Yes	No	No	No	No	No	No	2.5	Conservative	Medical treatment	No	No	7	10	No	No
5	Negative	-	Seville	B	IIIb	Acute	72	Female	Dissection	No	Yes	Yes	Yes	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	NA	Delayed	Endovascular surgery	NA	No	10	50	No	No
6	Negative	-	Seville	A	I	Acute	69	Male	Dissection	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	Yes	Yes	NA	Conservative	Medical treatment	Yes	No	1	1	Yes	No
7	Negative	-	Seville	B	IIIb	Acute	76	Male	Aneurysm	Yes	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	5	Delayed	Endovascular surgery	NA	No	8	20	No	No
8	Positive	*MYLK*	Seville	A	I	Acute	56	Male	Intramural hematoma	Yes	No	No	No	No	Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	4.1	Delayed	Open surgery	NA	No	8	18	No	Yes
9	Negative	-	Huelva	A	I	Acute	48	Male	Dissection	Yes	Yes	Yes	No	No	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	Yes	No	NA	Conservative	Medical treatment	NA	NA	1	1	Yes	No
10	Positive	*GAA*	Huelva	B	II	Acute	53	Male	Penetrating ulcer	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	No	NA	Conservative	Medical treatment	NA	NA	3	14	No	Yes
11	Negative	-	Seville	A	I	Acute	54	Male	Dissection	No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	Yes	No	NA	Emergent	Open surgery	Yes	No	40	40	Yes	No
12	Positive	*MYLK*	Seville	A	I	Acute	54	Male	Dissection	No	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	5	Urgent	Open surgery	Yes	Yes	28	58	No	Yes
13	Negative	-	Huelva	A	I	Acute	44	Male	Dissection	No	No	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	NA	Emergent	Open surgery	NA	No	3	13	No	No
14	Negative	-	Seville	A	II	Acute	58	Female	Dissection	No	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	No	NA	Urgent	Open surgery	NA	No	5	9	No	No
15	Positive	*FBN1*	Huelva	A	IIIb	Acute	42	Male	Dissection	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	No	4.5	Emergent	Open surgery	Yes	Yes	7	7	Yes	No
16	Negative	-	Huelva	B	IIIb	Acute	64	Male	Dissection	Yes	Yes	No	No	No	No	No	Yes	No	Yes	Yes	No	No	No	No	No	No	5	Emergent	Endovascular surgery	Yes	Yes	35	45	No	No
17	Negative	-	Seville	B	IIIb	Acute	53	Male	Dissection	Yes	No	Yes	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	4.4	Conservative	Medical treatment	No	No	7	13	No	No
18	Uncertain	*FBN1*	Seville	B	IIIb	Acute	59	Male	Dissection	No	Yes	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	No	2.5	Delayed	Endovascular surgery	No	No	5	20	No	Yes
19	Uncertain	*MYH11*	Huelva	A	II	Acute	57	Male	Dissection	No	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	NA	Delayed	Open surgery	NA	Yes	30	70	No	No
20	Negative	-	Huelva	A	I	Acute	62	Female	Dissection	Yes	Yes	Yes	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	NA	Emergent	Open surgery	NA	No	9	15	No	No
21	Negative	-	Seville	B	I	Acute	75	Female	Dissection	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	4.5	Conservative	Medical treatment	No	No	6	12	No	No
22	Uncertain	*MYLK*	Seville	B	IIIa	Chronic	59	Female	Aneurysm	Yes	Yes	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	4	Delayed	Endovascular surgery	No	No	3	9	No	No
23	Negative	-	Seville	A	I	Acute	36	Male	Dissection	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	No	No	No	No	No	No	NA	Urgent	Open surgery	Yes	No	6	10	No	No
24	Negative	-	Seville	A	I	Acute	49	Male	Intramural hematoma	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	NA	Delayed	Open surgery	No	No	14	37	No	No
25	Negative	-	Seville	A	II	Acute	54	Male	Dissection	No	Yes	Yes	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	2.8	Urgent	Open surgery	Yes	No	6	16	No	No
26	Negative	-	Seville	B	IIIa	Acute	55	Male	Penetrating ulcer	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	Yes	No	No	Yes	No	No	No	4	Emergent	Endovascular surgery	No	No	7	9	No	No
27	Positive	*ELN*	Seville	B	IIIb	Acute	54	Male	Dissection	Yes	No	No	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	3.3	Emergent	Endovascular surgery	Yes	Yes	4	4	Yes	No
28	Positive	*COL1A1*	Seville	A	IIIb	Acute	60	Male	Dissection	Yes	No	No	No	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	No	3.4	Urgent	Endovascular surgery	No	No	3	14	No	No
29	Uncertain	*NOTCH1*	Seville	A	I	Acute	63	Male	Dissection	Yes	Yes	No	No	No	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	No	No	Yes	3.6	Emergent	Open surgery	Yes	No	11	11	Yes	No
30	Negative	-	Seville	A	I	Acute	53	Male	Dissection	No	Yes	No	No	No	No	No	No	No	No	Yes	No	No	Yes	Yes	No	No	NA	Emergent	Open surgery	NA	No	31	44	No	No
31	Uncertain	*MYLK*	Huelva	B	IIIb	Acute	57	Male	Dissection	Yes	Yes	No	No	No	Yes	No	No	No	Yes	Yes	No	No	Yes	No	No	No	NA	Delayed	Endovascular surgery	NA	Yes	16	34	No	No
32	Negative	-	Seville	B	IIIb	Acute	62	Male	Dissection	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	No	NA	Conservative	Medical treatment	No	No	5	11	No	No
33	Negative	-	Seville	A	I	Acute	66	Female	Dissection	Yes	No	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	3.5	Emergent	Open surgery	Yes	No	8	8	Yes	No
34	Negative	-	Seville	B	IIIb	Acute	50	Male	Dissection	Yes	Yes	No	No	No	Yes	No	No	No	Yes	Yes	Yes	No	No	No	No	No	4.1	Urgent	Endovascular surgery	Yes	No	7	33	No	No
35	Positive	*ACTA2*	Seville	A	I	Acute	24	Female	Rupture aneurysm	Yes	No	No	No	No	No	No	No	No	No	No	No	Yes	No	Yes	No	Yes	3.5	Emergent	Open surgery	No	No	4	11	No	No
36	Negative	-	Seville	A	I	Acute	67	Male	Dissection	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	No	NA	Emergent	Open surgery	No	No	8	34	No	No
37	Negative	-	Seville	B	IIIa	Acute	63	Female	Penetrating ulcer	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	NA	Emergent	Endovascular surgery	No	No	5	8	No	No
38	Positive	*MYH11*	Seville	B	II	Acute	46	Female	Dissection	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	No	No	Yes	No	No	Yes	3.5	Emergent	Open surgery	No	No	6	25	No	Yes
39	Positive	*MYLK*	Seville	A	II	Chronic	27	Male	Aneurysm	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	4.1	Conservative	Medical treatment	No	No	2	7	No	No

40	Uncertain	*TGFBR2*	Seville	B	IIIb	Subacute	57	Male	Dissection	Yes	No	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	NA	Conservative	Medical treatment	NA	NA	11	18	No	No
41	Negative	-	Huelva	A	I	Acute	70	Female	Dissection	No	No	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	12.5	Emergent	Open surgery	No	No	5	15	No	No
42	Negative	-	Huelva	A	I	Acute	52	Male	Dissection	Yes	Yes	Yes	No	No	No	No	No	No	Yes	No	Yes	No	Yes	No	No	No	NA	Urgent	Open surgery	NA	Yes	37	48	No	No
43	Negative	-	Seville	A	I	Acute	50	Male	Dissection	No	No	No	No	No	No	No	No	No	Yes	No	No	No	Yes	No	Yes	No	4.7	Emergent	Open surgery	No	No	45	51	No	No
44	Positive	*ACTA2*	Seville	B	IIIb	Acute	46	Male	Dissection	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	6.2	Conservative	Medical treatment	No	Yes	7	16	No	No
45	Negative	-	Seville	B	IIIa	Acute	67	Female	Penetrating ulcer	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	NA	Emergent	Endovascular surgery	NA	No	3	6	No	No
46	Negative	-	Seville	B	IIIa	Chronic	69	Male	Dissection	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	4.5	Delayed	Endovascular surgery	No	No	2	6	No	No
47	Negative	-	Huelva	A	I	Acute	57	Male	Dissection	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No	No	No	No	5.4	Emergent	Open surgery	No	No	22	52	No	No
48	Uncertain	*NOTCH1*	Seville	A	II	Subacute	81	Female	Dissection	No	Yes	No	No	No	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No	No	5.8	Urgent	Open surgery	Yes	Yes	25	35	Yes	No
49	Uncertain	*GAA*	Seville	A	I	Acute	76	Male	Dissection	Yes	Yes	No	No	Yes	No	No	No	Yes	Yes	No	No	No	No	No	No	No	5.5	Delayed	Endovascular surgery	No	No	2	5	No	Yes
50	Negative	-	Seville	B	IIIb	Chronic	69	Male	Dissection	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	No	No	No	No	No	No	4.2	Delayed	Endovascular surgery	No	No	1	5	No	No
51	Negative	-	Seville	A	II	Acute	62	Female	Intramural hematoma	No	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	3.7	Urgent	Open surgery	No	No	9	NA	No	No
52	Uncertain	*ELN*	Seville	A	I	Acute	71	Female	Dissection	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	No	Yes	Yes	No	No	No	Yes	4.9	Urgent	Open surgery	Yes	No	10	23	No	No
53	Positive	*SLC2A10*	Huelva	A	II	Chronic	27	Male	Aneurysm	No	No	No	No	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	4.4	Delayed	Open surgery	Yes	Yes	19	NA	No	No
54	Negative	-	Seville	A	I	Acute	63	Female	Dissection	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	Yes	5.2	Emergent	Open surgery	Yes	No	9	9	Yes	No
55	Negative	-	Seville	B	I	Chronic	67	Male	Aneurysm	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	4.8	Delayed	Endovascular surgery	No	No	2	4	No	No
56	Negative	-	Salamanca	A	I	Acute	77	Male	Dissection	Yes	No	No	No	Yes	No	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	No	5	Emergent	Open surgery	Yes	Yes	24	24	Yes	No
57	Negative	-	Seville	A	IIIa	Chronic	74	Male	Dissection	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	No	Yes	No	No	No	Yes	4.7	Conservative	Medical treatment	Yes	No	5	4	Yes	No
58	Negative	-	Italy	A	I	Acute	61	Male	Dissection	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	No	Yes	No	Yes	No	4.2	Emergent	Open surgery	Yes	Yes	25	NA	No	No
59	Negative	-	Seville	A	I	Acute	67	Female	Intramural hematoma	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	Yes	4.2	Urgent	Open surgery	No	No	7	28	No	No
60	Uncertain	*ELN*	Lleida	A	I	Acute	47	Male	Dissection	No	No	No	No	No	No	No	No	No	Yes	Yes	Yes	No	Yes	No	Yes	No	4.1	Delayed	Open surgery	Yes	Yes	25	27	No	No
61	Positive	*MYH11*	Seville	A	IIIb	Acute	39	Male	Dissection	No	No	No	No	No	No	No	No	Yes	No	Yes	Yes	No	No	No	Yes	No	2.6	Emergent	Open surgery	Yes	No	51	71	No	Yes
62	Uncertain	*FBN2*	Seville	A	II	Acute	68	Female	Intramural hematoma	Yes	Yes	No	No	No	No	No	No	No	Yes	No	No	Yes	No	Yes	No	No	4.1	Emergent	Open surgery	Yes	Yes	5	62	No	No
63	Positive	*FBN1*	Seville	B	IIIb	Subacute	57	Male	Penetrating ulcer	No	Yes	Yes	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	No	4.5	Delayed	Endovascular surgery	No	No	6	7	No	Yes
64	Positive	*NF1*	Seville	A	I	Acute	59	Male	Dissection	Yes	No	No	No	No	No	No	No	No	No	No	Yes	No	No	No	No	Yes	5.2	Conservative	Medical treatment	Yes	No	1	2	Yes	No
65	Positive	*COL5A2*	Huelva	A	I	Acute	55	Male	Dissection	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	No	No	Yes	No	No	No	4.1	Emergent	Open surgery	Yes	No	15	NA	No	No
66	Negative	-	Seville	B	IIIb	Acute	68	Male	Rupture aneurysm	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	No	Yes	Yes	No	Yes	4.2	Urgent	Endovascular surgery	No	No	2	32	Yes	No
67	Positive	*FBN1*	Huelva	A	IIIa	Chronic	16	Male	Aneurysm	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	6.49	Delayed	Open surgery	No	No	3	9	No	No
68	Positive	*MYH11*	Huelva	A	I	Acute	55	Male	Dissection	No	Yes	No	Yes	No	No	No	No	No	Yes	Yes	No	No	No	No	No	No	4.8	Emergent	Open surgery	Yes	No	7	20	No	No
69	Positive	*FBN1*	Huelva	A	I	Acute	38	Female	Dissection	No	Yes	No	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	No	No	4.5	Emergent	Open surgery	No	NA	NA	NA	NA	Yes
70	Negative	-	Seville	B	IIIb	Chronic	49	Male	Dissection	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	5.1	Delayed	Endovascular surgery	No	Yes	3	8	No	No
71	Uncertain	*MYH11*	Seville	A	I	Acute	80	Female	Intramural hematoma	No	Yes	Yes	No	Yes	No	No	No	No	Yes	Yes	No	No	No	No	No	Yes	4.6	Emergent	Open surgery	No	No	8	21	No	No
72	Positive	*TGFBR2* / *TGFBR1*	Huelva	A	I	Acute	42	Male	Dissection	Yes	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No	No	No	No	6.5	Emergent	Open surgery	No	No	7	12	No	No
73	Negative	-	Seville	B	IIIb	Subacute	72	Male	Aneurysm	No	Yes	No	No	Yes	No	No	No	No	Yes	No	No	No	No	No	No	No	7.3	Delayed	Endovascular surgery	No	No	5	13	No	No

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NA, not available.

Genetic classification was based on the identification of pathogenic variants (positive cases), variants of unknown significance (uncertain cases) and the absence of potentially causal variants (negative cases). Acute dissection was diagnosed when clinical presentation has lasted for 15 days or less, while subacute refers to a symptom onset within 15 to 30 days, and symptom duration greater than 1 month was considered to be chronic.