

주최·주관 대한심장혈관흉부외과학회

2024 대한심장혈관흉부외과학회

제56차 추계학술대회

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# Diagnosing Hereditary Thoracic Aortic Disease by Targeted sequencing of Human Aorta Tissue

## Background

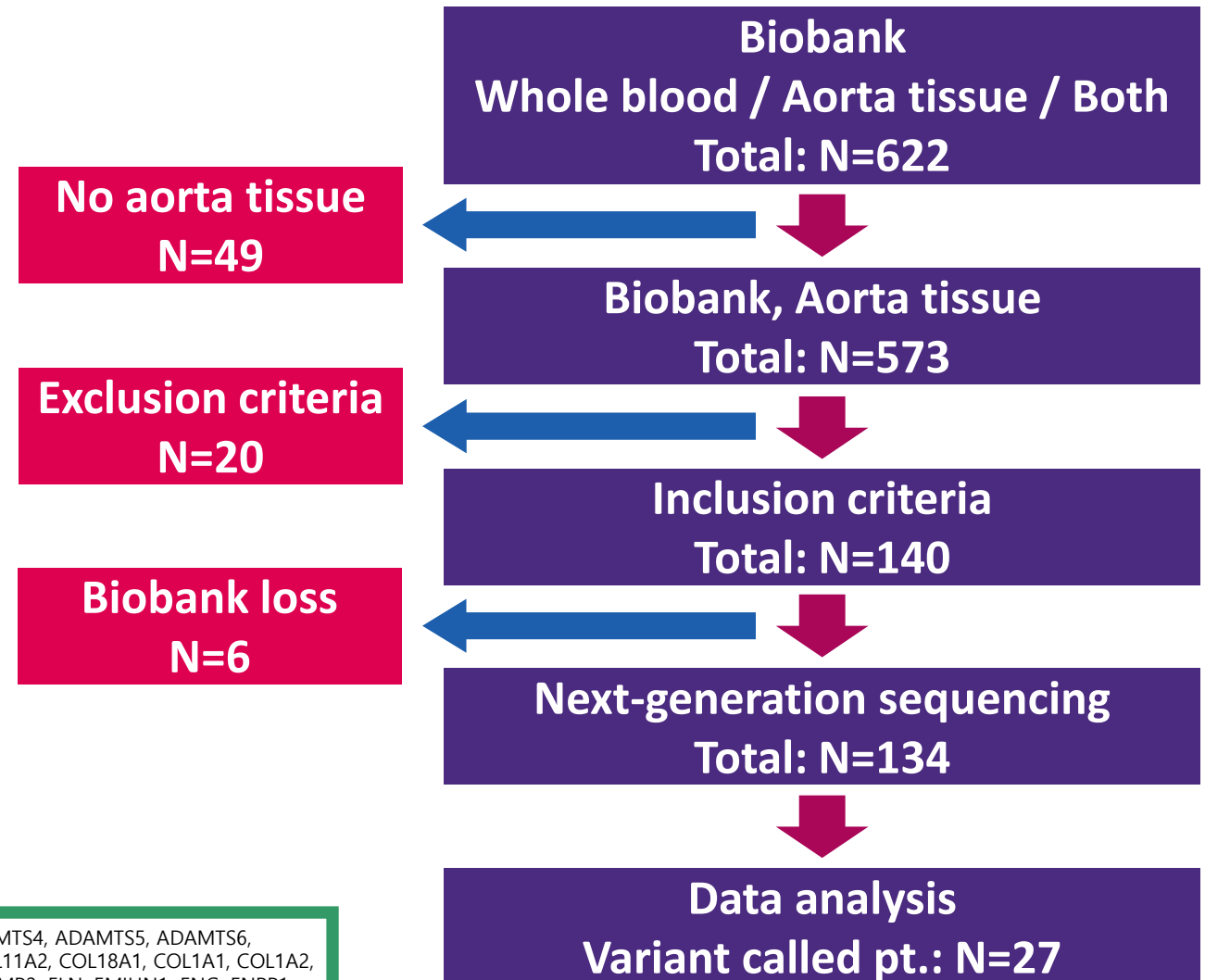
- Approximately 20% of thoracic aortic aneurysm (TAA) patients are related to genetic or heritable conditions, which we call hereditary thoracic aortic disease (HTAD).
- The emergence of next-generation sequencing (NGS) technologies gave milestones in our understanding of rare diseases such as HTAD.
- Despite the advance in sequencing technologies, HTAD is hard to diagnose in real world due to,
  - ✓ Refuse of genetic testing such as financial problems
  - ✓ Discrepancy of clinical data and genomic data such as de novo mutations or mosaicisms
  - ✓ Various expressivity and incomplete penetrance

## Purpose

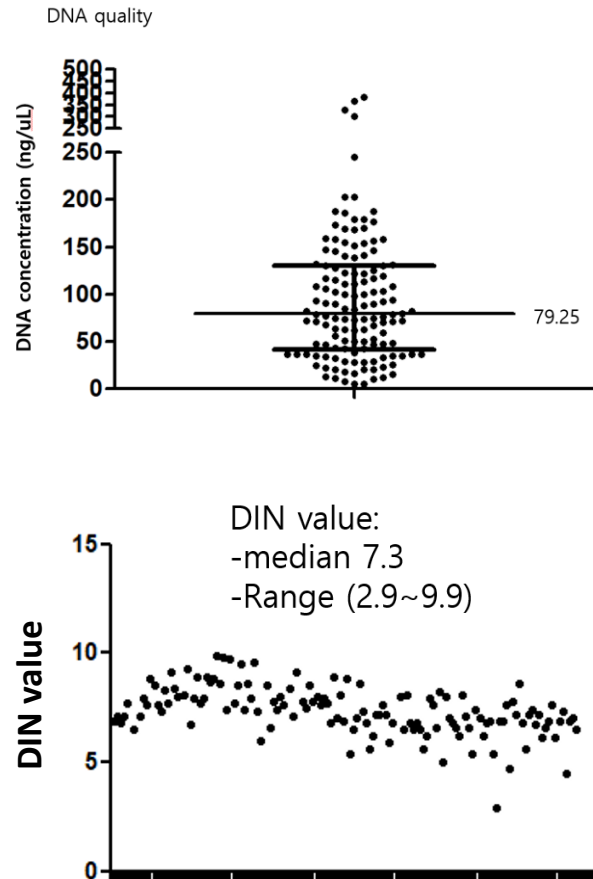
- To diagnose HTAD by retrieving human aorta tissues in biobank.
- To diagnose HTAD by targeted panel sequencing of human aorta tissues.

- From May 2016 to November 2021
- Single center Study
- Inclusion criteria
  - ✓ Family history of aortic disease
  - ✓ Age  $\leq 45$
  - ✓ Annuloaortic ectasia (AAE)
  - ✓ Bicuspid aortic valve (BAV)
  - ✓ Patent ductus arteriosus (PDA)
  - ✓ Polycystic kidney disease (PKD)
  - ✓ Previously classified as VUS (N=17)
- Exclusion criteria
  - ✓ Previously classified as LP/P (N=20)
- Targeted panel genes: 96 genes

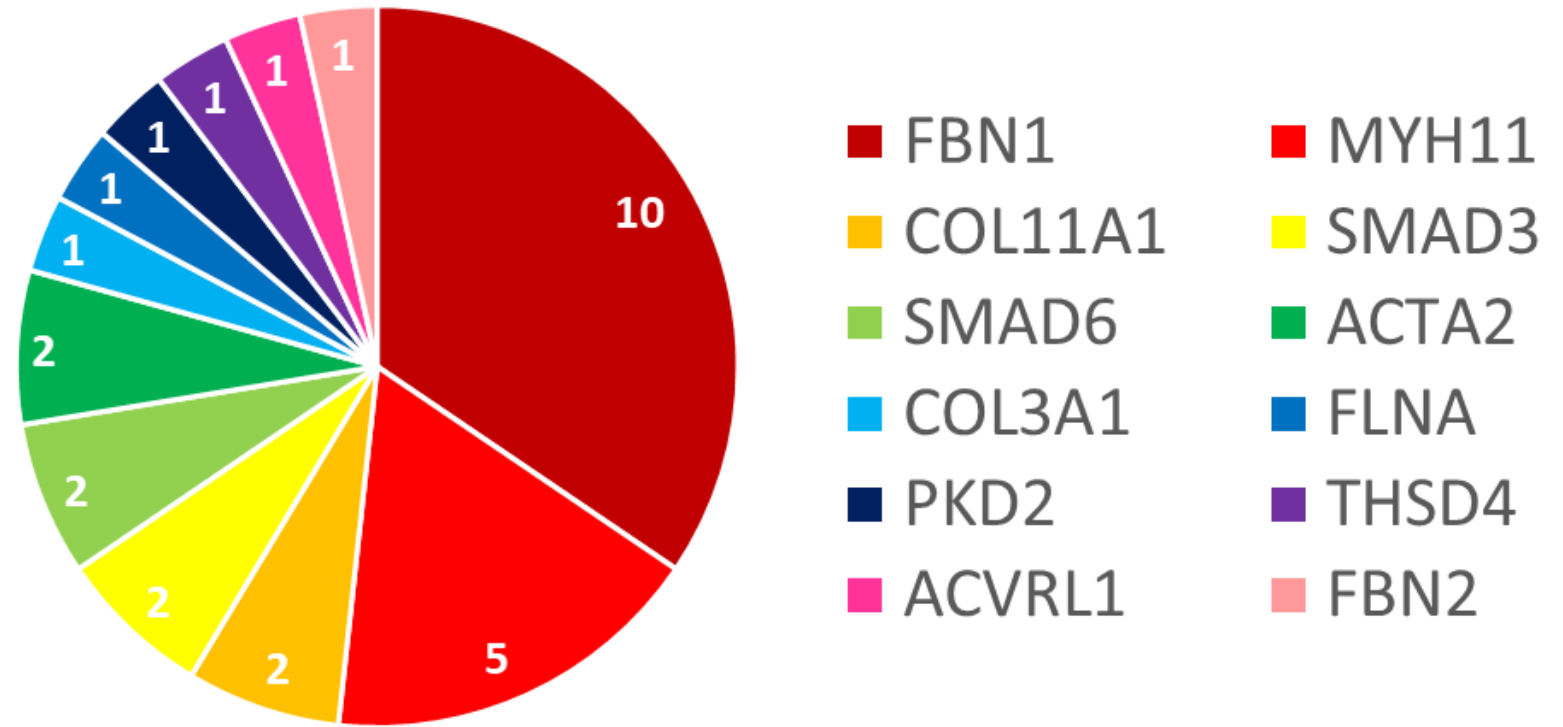
ABCC6, ABL1, ACTA2, ACVR1, ACVRL1, ADAMTS1, ADAMTS10, ADAMTS17, ADAMTS19, ADAMTS2, ADAMTS4, ADAMTS5, ADAMTS6, ADAMTSL4, ALDH18A1, ARIH1, ATP6V0A2, ATP7A, B3GAT3, B4GALT7, BGN, CBS, CHST14, COL11A1, COL11A2, COL18A1, COL1A1, COL1A2, COL2A1, COL3A1, COL4A1, COL4A5, COL5A1, COL5A2, COL9A1, COL9A2, COL9A3, COLGALT1, DBP, EFEMP2, ELN, EMILIN1, ENG, ENPP1, FBLN5, FBN1, FBN2, FKBP14, FLCN, FLNA, FOXE3, GATA5, HCN4, HEY2, HNRNP, IPO8, JAG1, KCNN1, LOX, LTBP1, LTBP2, LTBP3, MAT2A, MED12, MFAP5, MSTN, MYH11, MYLK, MYLK2, NOTCH1, PKD1, PKD2, PLOD1, PLOD3, PRDM5, PRKG1, ROBO4, SKI, SLC2A10, SLC39A13, SMAD2, SMAD3, SMAD4, SMAD6, TGFB2, TGFB3, TGFB1, TGFB2, THSD4, TIMP1, TIMP3, TNXB, UPF3B, VCAN, ZDHHC9, ZNF469



**Fig.1 QC (Quality Control) of Aorta tissue**



**Fig.2 Variant called genes of HTAD**  
Total genes: n=29



\*Variant: variants classified as VUS, LP and Pathogenic by 2015 ACMG guideline

Table 1. Clinical and Genetic Data of Patients with VUS, LP, and Pathogenic Variants (\* Variant: variants classified as VUS, LP and P by 2015 ACMG guideline)

No	Sex	Age	Diagnosis	Operation	F.Hx	AAE	BAV	PDA	PKD	Gene	Nucleotide change	Protein change	Variant	Effect	ACMG	OMIM
1	M	29	AAE	Bentall	+	+	-	-	-	FBN1	c.4927dup	p.(Thr1643AsnfsTer5)	indel	Frameshift	LP/P	MFS
2	M	35	TAAA	TAAA	-	+	-	-	-	FBN1	c.6295T>C	p.(Cys2099Arg)	SNP	Missense	LP/P	MFS
3	F	57	AAE	VSARR	+	+	-	-	-	FBN1	c.4927dup	p.(Thr5643AsnfsTer5)	indel	Frameshift	LP/P	MFS
4	F	29	ATAAD	VSARR+TAR	+	+	-	-	-	FBN1	c.6296G>T	p.(Cys2099Phe)	SNP	Missense	LP/P	MFS
5	F	34	AAE	VSARR	+	+	-	-	-	FBN1	c.4911C>G	p.(Tyr1637Ter)	SNP	Nonsense	LP/P	MFS
6	M	36	ATAAD	2PAR	+	-	-	-	-	COL3A1	c.2689G>A	p.(Gly897Ser)	SNP	Missense	LP/P	vEDS
7	M	45	CTAAD	Bentall	-	+	-	-	-	FLNA	whole gene duplication		CNV		VUS	Cardiac valvular dysplasia
8	M	48	CTAAD	Bentall+2PAR	+	+	-	-	-	SMAD3	c.695G>T	p.(Trp232Leu)	SNP	Missense	VUS/LP→LP	LDS3
9	M	48	BAV	2PAR	-	-	+	-	-	COL11A1	c.2758C>A	p.(Pro920Thr)	SNP	Missense	VUS	Stickler syndrome
10	M	53	CTAAD	Bentall+TAR	-	+	-	-	-	SMAD6	exon 1 deletion		CNV		VUS	Aortic valve disease 2
11	M	56	AAE	VSARR+TAR	-	+	+	+	-	SMAD6	exon 1 deletion		CNV		VUS	Aortic valve disease 2
12	F	63	ATAAD	TAR	-	+	-	-	-	MYH11	c.3719T>G	p.(Leu1240Arg)	SNP	Missense	VUS/LP	Aortic aneurysm, familial thoracic 4
13	F	65	ATAAD	2PAR	-	+	-	-	-	FBN1	c.4588C>T	p.(Arg1530Cys)	SNP	Missense	LP/P	MFS
14	F	36	ATAAD	VSARR+TAR	+	+	-	-	-	ACTA2	c.739G>A	p.(Gly247Arg)	SNP	Missense	VUS/LP→LP	Aortic aneurysm, familial thoracic 6
15	M	60	AAE	VSARR	-	+	-	-	-	FBN1	c.6695G>A	p.(Cys2232Tyr)	SNP	Missense	LP/P	MFS
16	F	64	ATAAD	VSARR+TAR	+	+	-	-	-	FBN1	c.5431G>A	p.(Glu1811Lys)	SNP	Missense	LP/P	MFS
17	F	64	ATAAD	1PAR	-	-	-	-	+	PKD2	exon 3-5 deletion		CNV		LP/P	PKD2
18	M	36	CTAAD	VSARR+1PAR	-	+	-	+	-	MYH11	c.4661_4681del	p.(Glu1554_Asp1560del)	indel		VUS	Aortic aneurysm, familial thoracic 4
19	F	37	AAE	VSARR	-	+	-	-	-	COL11A1	c.3688C>G	p.(Gln1230Glu)	SNP	Missense	VUS	Stickler syndrome
20	M	41	ATAAD	VSARR+TAR	-	+	-	+	-	ACTA2	c.338A>G	p.(Asn113Ser)	SNP	Missense	VUS	Aortic aneurysm, familial thoracic 6
21	M	50	ATAAD	VSARR+2PAR	-	+	-	-	-	MYH11	whole gene duplication		CNV		VUS	Aortic aneurysm, familial thoracic 4
22	M	51	ATAAD	VSARR+TAR	-	+	-	-	-	FBN1	c.1147G>A	p.(Glu383Lys)	SNP	Missense	VUS/LP→LP	MFS
23	M	61	AAE	VSARR+2PAR	-	+	+	-	-	THSD4	c.1862G>A	p.(Trp621Ter)	SNP	Nonsense	VUS/LP→LP	Aortic aneurysm, familial thoracic 12
24	F	67	AAE	VSARR+TAR	-	+	-	-	-	MYH11	c.4358T>G	p.(Phe1453Cys)	SNP	Missense	VUS	Aortic aneurysm, familial thoracic 4
25	M	42	ATAAD	VSARR+TAR	-	+	-	-	-	MYH11	c.3391C>T	p.(Arg1131Trp)	SNP	Missense	VUS	Aortic aneurysm, familial thoracic 4
26	F	46	AAE	VSARR	-	+	-	-	-	ACVRL1	c.936C>G	p.(His312Gln)	SNP	Missense	LP/P	Telangiectasia, hereditary hemorrhagic, type 2
										FBN1	c.2529del	p.(Ile844SerfsTer3)	indel	Frameshift	LP/P	MFS
27	F	37	ATAAD	VSARR+TAR	+	+	-	-	-	FBN2	c.6881-2A>G		SNP	Splice site	LP/P	Contractural arachnodactyly, congenital
										SMAD3	c.1153A>G	p.(Arg385Gly)	SNP	Missense	VUS/LP→LP	LDS3

\*\* F.Hx, Family history; Annuloaortic ectasia; BAV, Bicuspid aortic valve; PDA, Patent ductus arteriosus; PKD, Polycystic kidney disease; ATAAD, Acute type A aortic dissection; CTAAD, Chronic type A aortic dissection; TAAA, Thoracoabdominal aortic aneurysm (repair); VSARR, Valve sparing aortic root reimplantation; Bentall, Bentall operation; 1PAR, 1 partial arch replacement; 2PAR, 2 partial arch replacement; TAR, total arch replacement; MFS, Marfan syndrome; vEDS, vascular type Ehlers-Danlos syndrome; LDS3, Loeys-Dietz syndrome type 3; SNP, single nucleotide polymorphism; CNV, copy number variation; indel, insertion-deletion; VUS, variant of uncertain significance; LP, likely pathogenic; P, pathogenic

- Retrieving human aorta tissue samples from biobank had good quality control for DNA sequencing (DIN: 7.3, range 2.9~9.9).
- Due to the strategy of aortic surgery, human aorta tissue can be a good source for genomic data analysis.
- Variant calling was done at 27 pts (20.1%) by data analysis.
  - ✓ 12 pts (9.0%) were classified as LP/P.
  - ✓ 6 pts (4.5%) were classified as VUS/LP and with clinical data 5 pts (3.7%) were reclassified as LP/P.
  - ✓ 10 pts (7.4%) were classified as VUS and further reanalysis may be required.
- Further studies must be required for association between COL11A1 gene (OMIM: Stickler syndrome) and HTAD.
- HTAD can be diagnosed in patients whose first aortic event occurred at the age over 60.
- Multidisciplinary team approach for precision medicine must be important in diagnosing HTAD to interpretate the discrepancy between clinical data and genomic data.