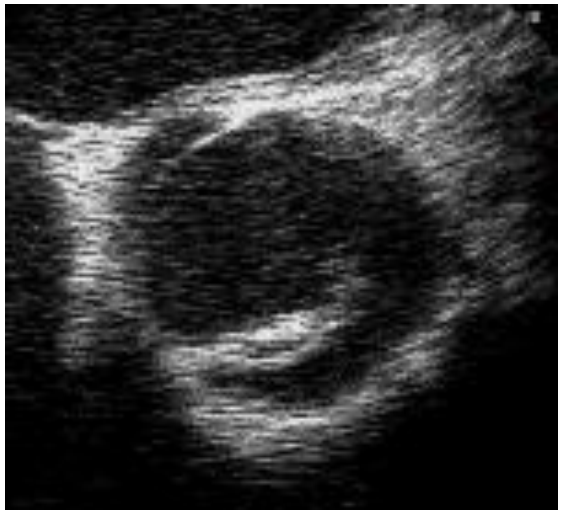
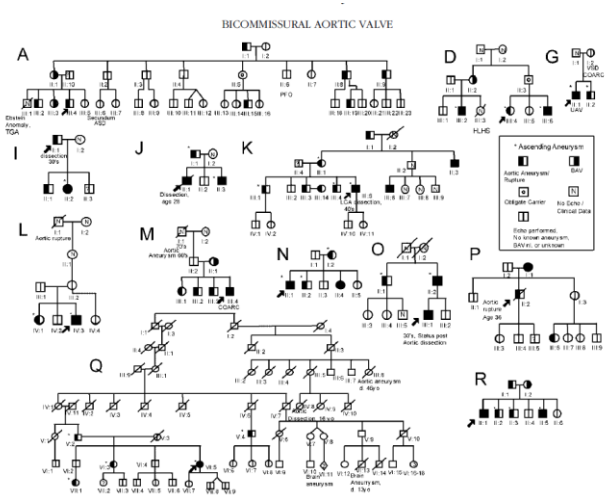
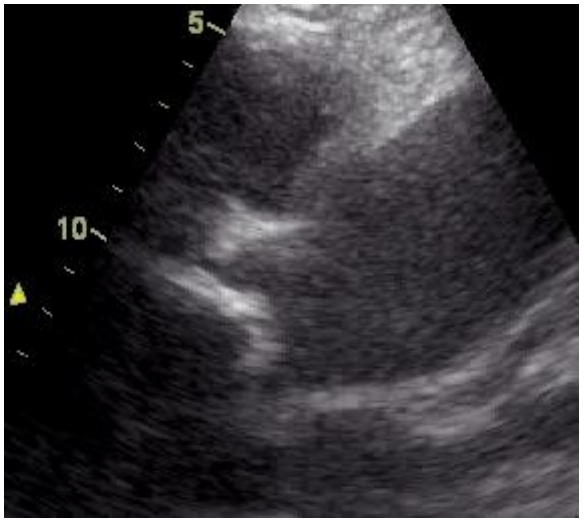
l'institut du thorax

EuroValves, Liège, 28-29 Oct 2021

Indication of familial screening in Bicuspid Aortic Valve







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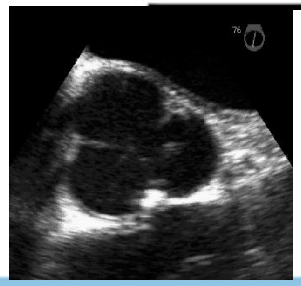
Bicuspid aortic valve

⇒ up to 1-2%

⇒ Sex ratio 3-4M/1

Bicuspid Aortic Valve Types and Phenotypes



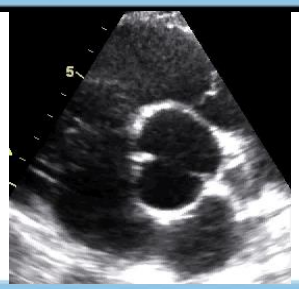
Fused BAV (90-95%)

- 3 aortic sinuses
- 2 cusps: Usually different size/shape with asymmetric or symmetric non-fused commissural angle
- 2 commissures
- Raphe: Common, visible or not

↓

Specific phenotypes of fused BAV

- Right-left cusp fusion (70-80%)
- Right-non cusp fusion (20-30%)
- Left-non cusp fusion (3-6%)
- Indeterminate cusp fusion



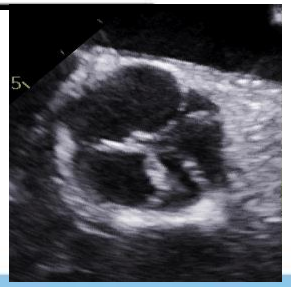
2-Sinus BAV (5-7%)

- 2 aortic sinuses
- 2 cusps: Roughly same size/shape with symmetric non-fused commissural angle
- 2 commissures
- Raphe: No

↓

Specific phenotypes of 2-sinus BAV

- Latero-lateral (most common)
- Anterior-posterior



Partial-fusion BAV (%?) (forme fruste)

- 3 aortic sinuses
- 3 cusps: Usually symmetric
- 3 "apparent" commissures where 2 are normal and the third is fused <50%
- Raphe: Small, mini-raphe

↓

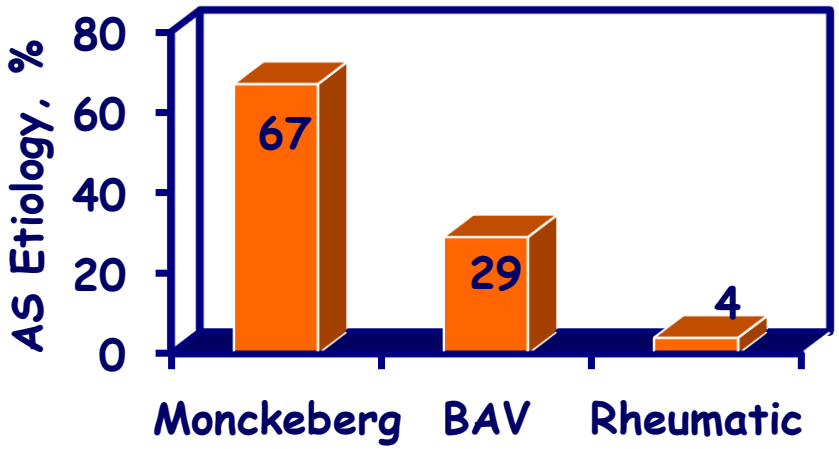
Specific phenotype of partial-fusion BAV

- Partial (<50%) fusion of one commissure

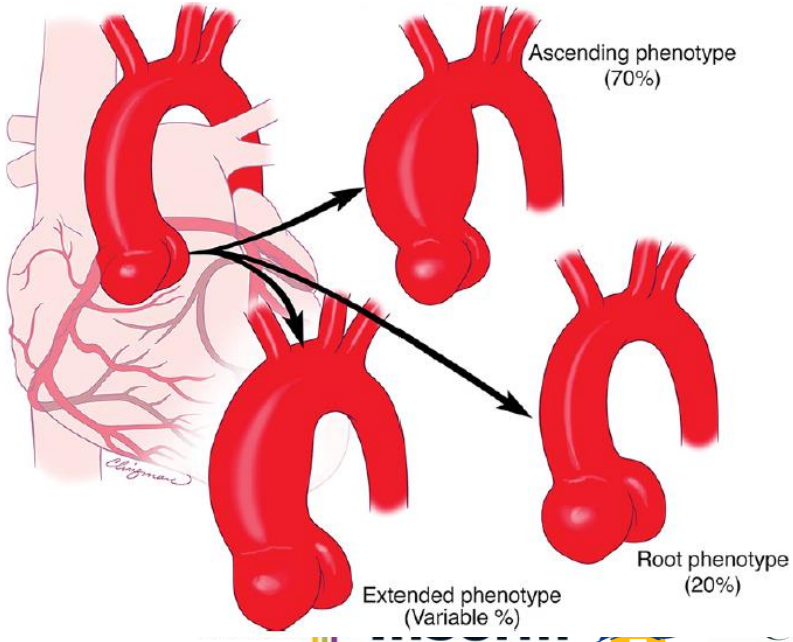
Michelena H, Radiology CV Img 2021; 3: 1-29

BAV Complications

- Valve dysfunction (AS-AR)
  - 30-50% over life
- Endocarditis
  - 0.3 to 2% per year
- Aorta dilatation
  - 20-40% of BAV
  - Also in relatives w/o BAV
  - Aorta aneurysm (10-20%)
  - Dissection (0.1% per year)

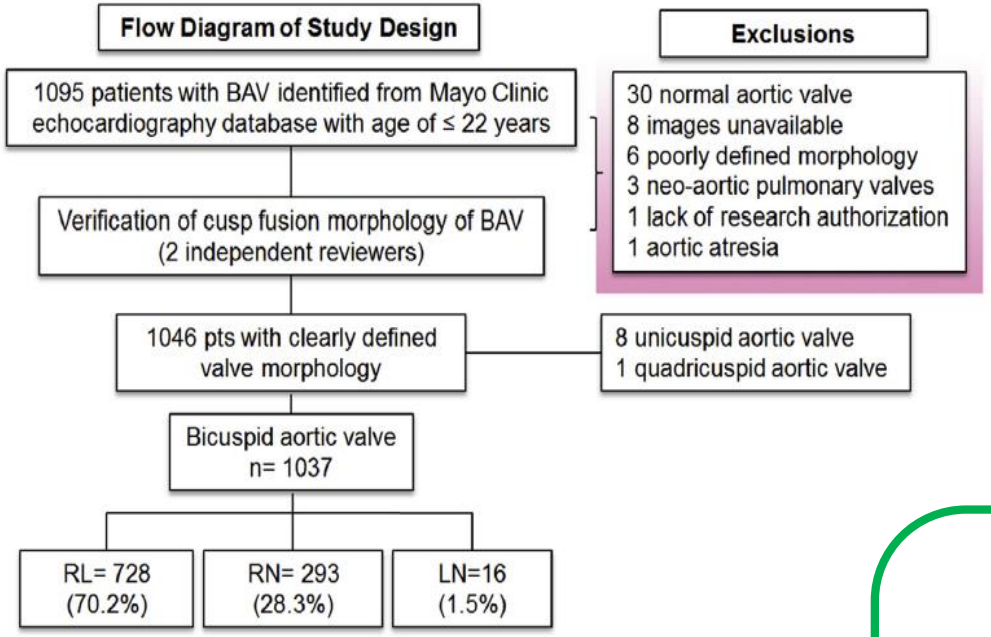


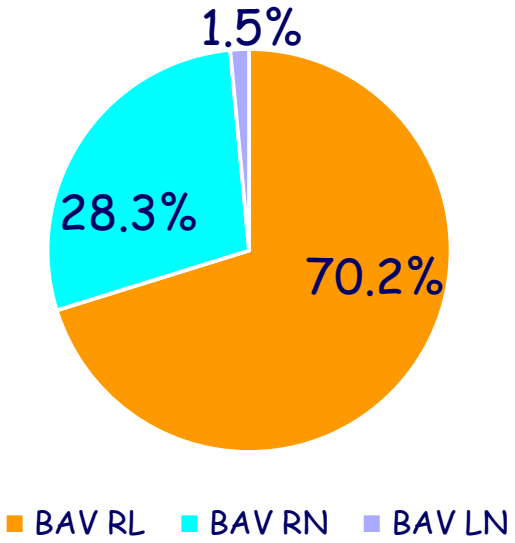
Three types of aorta dilatation

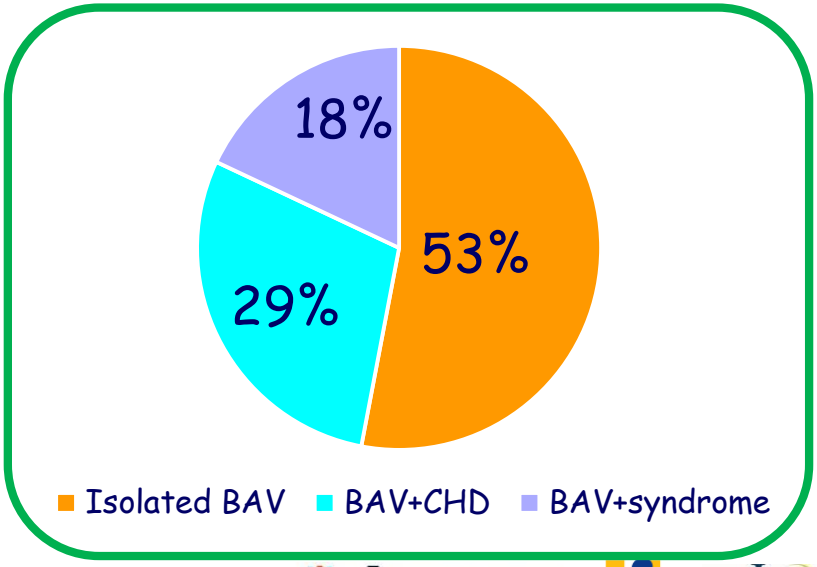


Verma S, NEJMed 2014; 370: 1920-9

BAV morphology and associated CHD

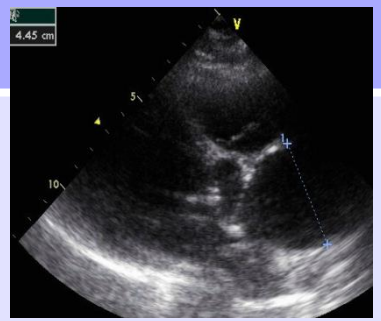
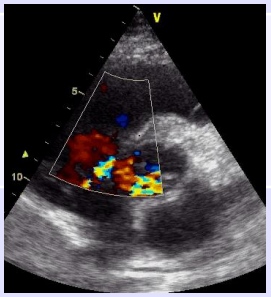
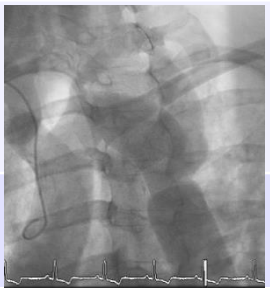
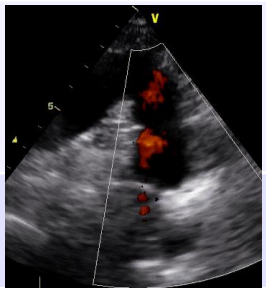






Niaz T, JASE 2018; 31: 194-200

Cardiac defects associated with BAV

Associated cardiac defects	%
Thoracic aorta dilatation 	20-40
VSD 	14
Mitral valve abnormalities	11
Coarctation  	7
PDA	8.5

Cripe L, JACC 2004; 44: 138-43
Verma S, NEJMed 2014; 370: 1920-9
Bravo-Jaimes K, Prog CV Dis 2020; 63: 398-406

BAV/TAA frequency in FdRelatives

Name	Number of probands /number of 1st degree relatives	BAV/isolated TAA = Overall
Huntington K, JACC 1997	30/186	9.1%
Cripe, JACC 2004	50/259 1st and 2nd	9.2%
Panayotova R, J Heart Valve Dis 2013	24/52	8%
Robledo-Carmona J, Int J Cardiol 2013	100/348	4.6%
Cozijnsen L, Int J Cardiol 2018	54/134	6% / 7.5% = 13%
Galian-Gay L, Heart 2019	256/724	6.4% / 9.6% = 16%
Massardier C, Ped Cardiol 2020	213/482	6.6% / 2.9%

35 to 50% families have at least one relative with BAV
10 to 13 individuals to be screened for one BAV

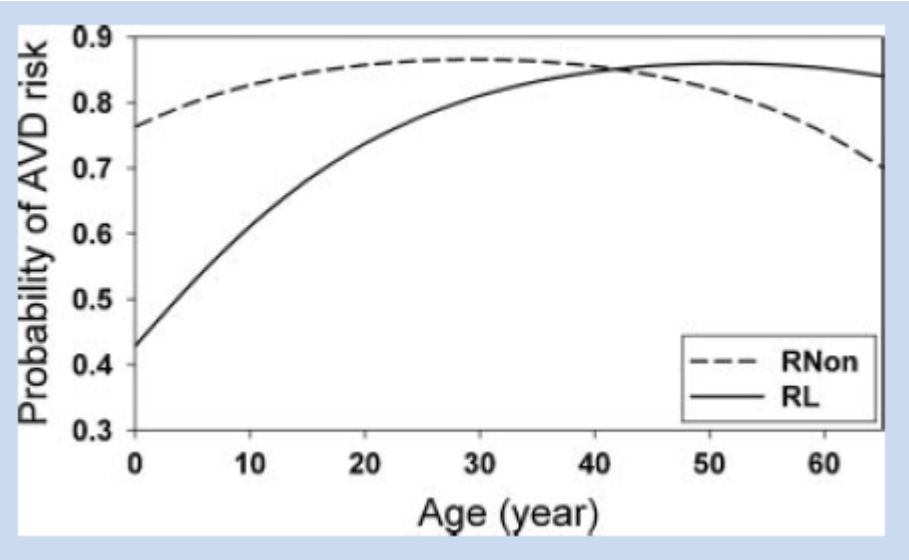
What is the mode of inheritance ?

- Autosomal dominant inheritance is the main mode
- Incomplete or reduced penetrance
- Only ≈ 10% of relatives have a BAV phenotype
- Turner syndrome (X0): 30% of BAV
- X-chromosome inheritance reported in FLNA-related VHD

Le Tourneau T, Eur Heart J; 2018: 39: 1269-77
Prakash SK, JACC 2014; 64: 832-9

Heritability of BAV pattern ?

- Concordance by chance: ≈ 60%
- Concordance of BAV phenotype ?
  - Concordance: 70-75%
  - Discordance: 25-30%



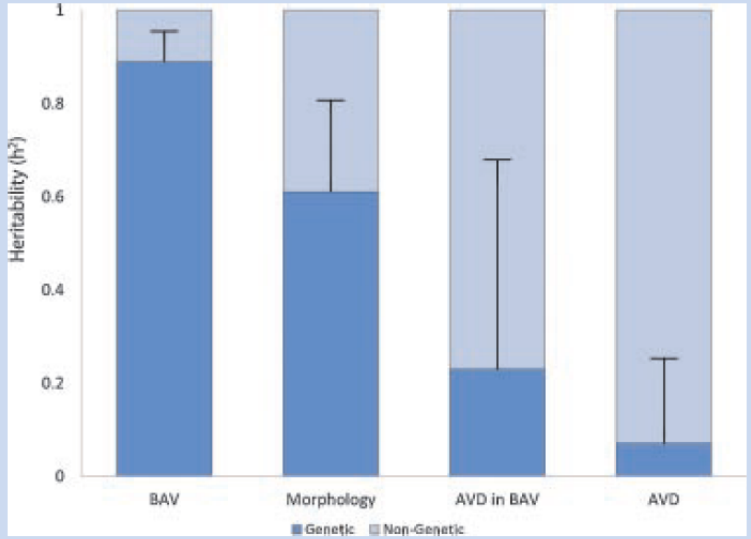


FIG. 2. The relative contribution of genetic and nongenetic factors in the manifestation of BAV and AVD. Heritability (h^2) estimates are shown as percentage ± SD. While BAV is determined largely by genetic effects (dark blue), the phenotypic variability of AVD is largely determined by nongenetic factors (light blue). [Color figure

Huntington K, JACC 1997; 30: 1809-12
Calloway TJ, Am J Med Genet 2011; 155A: 1015-20

Genetics of BAV: Causal genes

Genes associated with BAV.

Gene	Locus	OMIM disease	Function	Size and Type of Cohort
NOTCH1	9q34.3	Adams-Oliver syndrome 5, Aortic valve disease 1	Endocardial cushion development, aortic valve calcification	Family-based genome-wide scan, including 14 BAV individuals
SMAD6	15q22.31	Aortic valve disease 2	Cardiac valves development and outflow tract septation	Targeted resequencing in 441 BAV/TAA cohort
GATA4	8p23.1	Atrial septal defect 2, atrioventricular septal defect 4, tetralogy of Fallot, ventricular septal defect 1	Myocardial differentiation and function	Sequencing of 150 nonsyndromic BAV individuals
GATA5	15q25-q26.1, 20q13.13	Congenital heart defects, multiple types, 5	Extracellular matrix remodeling and morphogenesis of valve leaflets	Sequencing of 110 nonsyndromic BAV individuals
GATA6	18q11.2	Tetralogy of Fallot, patent ductus arteriosus, atrial septal defect 9, atrioventricular septal defect 5	Outflow tract and subpulmonary myocardial development	Family-based sequencing study including 152 BAV individuals
ROBO4	11q24.2	Aortic valve disease 8	Outflow tract development and integrity of ascending aorta	Family-based targeted sequencing including 10 BAV individuals
MAT2A	2p11.2		Smooth muscle cell function and development	Family-based whole exome sequencing including 8 individuals with TAA with or without BAV
ADAMTS19	5q23.3		Perturbs shear stress signaling in valvular endothelial cells, increasing cellularity and proteoglycan deposition	Family-based exome sequencing, including 8 affected individuals with early-onset valvular heart disease

Freeze SL, J Genet Counsel; 2016: 25: 1171-8
Bravo-Jaimes K, Prog CV Dis 2020; 63: 398-406
Gould RA, Nature Genet 2019; 51: 42-50
Wunnemann F, Nature Genet 2020; 52: 40-47

ROBO4 (endothelial function)
ADAMTS 19 (VIC)
Piezo
FLNA (mechano-transduction, primary cilia function)

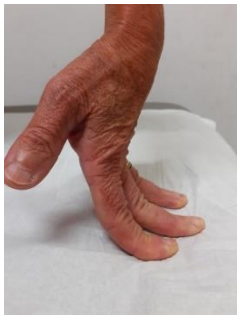
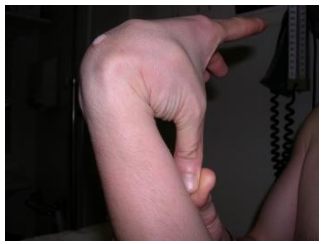
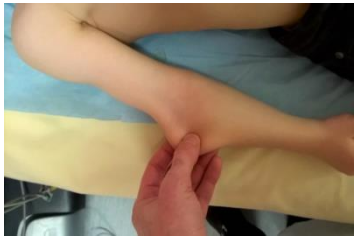
BAV in pathology

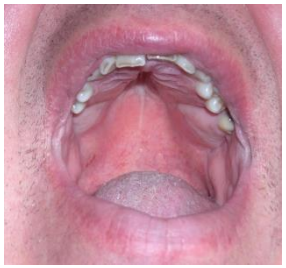
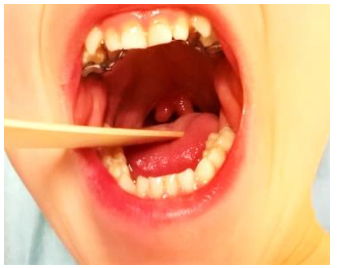
Congenital Cardiopathy	% of BAV Type of BAV	Connective syndrome	% of BAV Type of BAV
Turner (X0)	>30% 87% RL	Loeys-Dietz (TGFBR1, R2, TGFB2)	10%
Shone	60-70% 94% RL	Marfan (FBN1)	2-4%
DiGeorge (del 22q11.2)	100% RL	TAA (ACTA2)	3%
Down (duplication 21)	63% RN		
Coarctation	>50%		
Hypoplastic LHS	17%		

Bravo-Jaimes K, Prog CV Dis 2020; 63: 398-406
Niaz T, JASE 2018; 31: 194-200

Screening for syndromic features

- TTE: MVP, Aorta dilatation, CHD
- Family Hx aorta aneurysm/dissection
- Clinical features (2 min exam):
  - Thumb and wrist sign, flat feet
  - Myopia ≥ 3 DO
  - outward or inward breastbone
  - Benign hypermobility joint syndrome (spontaneous dislocation patella, thumb…)
  - long fingers, height/arms ratio
  - Scoliosis, skin hyperlaxity
  - narrow palate with crowded teeth

Pepe G, Intern emerg Med 2021; 16: 609-15

Recommendations for BAV screening

Guideline	First author /Journal	Familial screening Recommendations
2021 ESC/EACTS Guidelines for the management of VHD	Vahanian A, Eur Heart J 2021	It is appropriate to have an echocardiographic screening of first-degree relatives.
2020 ACC/AHA Guideline for the Management of Patients With VHD	Otto C, Circulation 2021	First d. relatives screening TTE might be considered to look for a BAV or a dilation of aortic sinuses/ascending aorta (2b)
Aorta: AATS consensus Guidelines 2018	Borger M, JTCVS 2018	First-degree relatives screening with echocardiography
2016 BAV: a Review with Recommendations for Genetic Counseling	Freeze SL, J Genet Counsel 2016	advocate for family screening for all cases of BAV
2014 Canadian Cardiovascular Society Position Statement on the Management of Thoracic Aortic Disease	Boodhwany M, Can J Cardiol 2014	First-degree relatives screening is suggested with a TTE for BAV and/or ascending aorta dilation including in the pediatric age range

Baibars M, Oschner J 2018; 18: 9-11

Conclusion

- TTE screening in first degree relatives of all patient with BAV
- Clinical interview to detect familial valvular or aortic pathologies, congenital cardiopathies, syndrome features
- Quick clinical examination (2 min) to look for the main syndrome features
- Refer to a geneticist only patients who have features of genetic syndrome, complex congenital heart defect, or heritable thoracic aorta dilatation

Freeze SL, J Genet Counsel; 2016: 25: 1171-8
Hiratzka LF,JACC 2016; 67: 724-31
Bravo-Jaimes K, Prog CV Dis 2020; 63: 398-406

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Thank you for your attention

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