Single Institution Analysis of Genetic Testing for Patients with Thoracic Aortic Aneurysm Disease

Implications for Clinical Efficacy of Current ACC/AHA Genetic testing Guidelines

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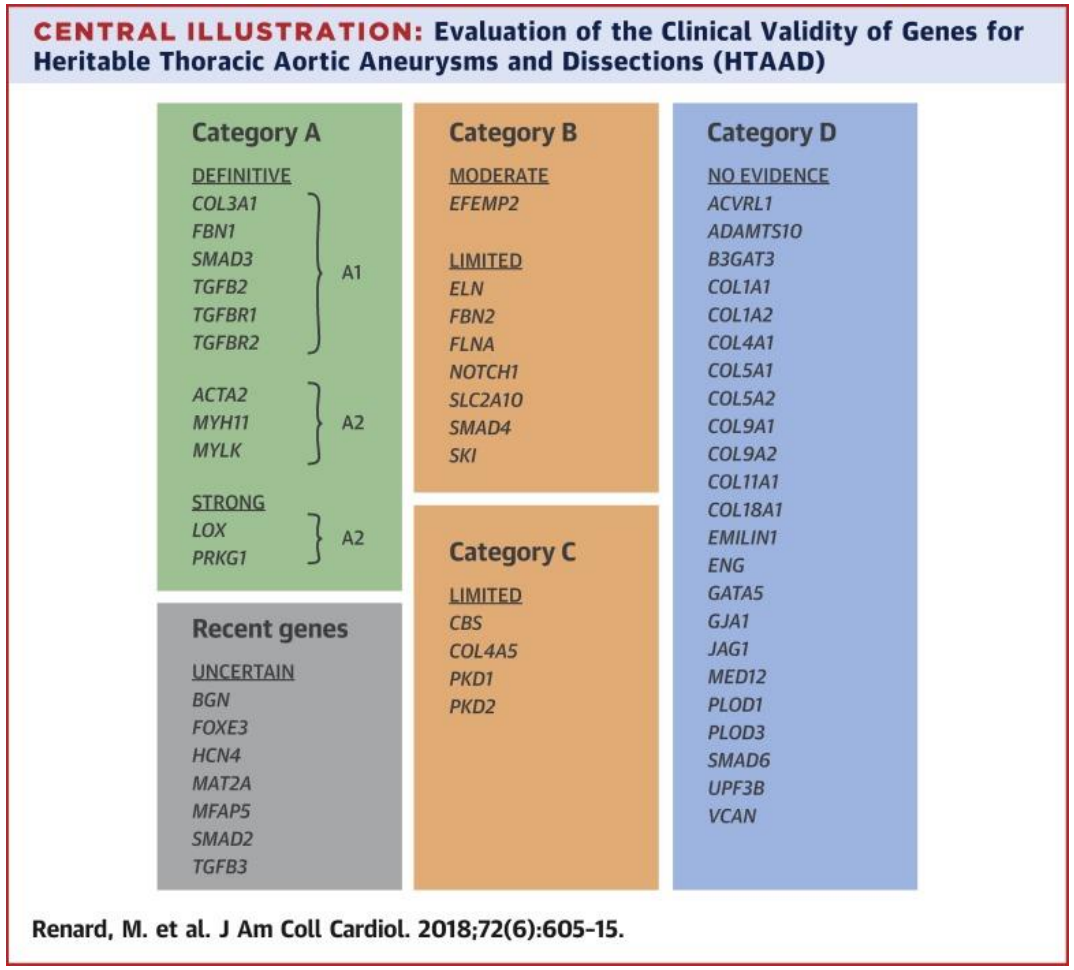
Background

- A significant proportion of thoracic aortic aneurysm (TAA) have a hereditary component
- Identification of pathogenic mutations through genetic testing greatly influences diagnostic and management strategies for patients and their families
- The “2022 ACC/AHA Guideline for the Diagnosis and Management of Aortic Disease” recommends genetic testing for thoracic aortic aneurysm patients with:
  1. Age Under 60 Years
  2. Presence of Syndromic Features of Connective Tissue Disease (CTD)
     - Marfan Syndrome, Loeys-Dietz Syndrome, or Vascular Ehlers-Danlos Syndrome
  3. Relevant Family History
     - First- or second-degree relative with thoracic aortic disease, peripheral/intracranial aneurysms, or unexplained sudden death at relatively young age

Isselbacher et al., 2022

Background (continued)



- ClinGen Aortopathy Working Group classified genes by severity and risk of progression:
  - Category A: Definitively associated with heritable-thoracic aortic disease (TAD)
  - Category B: Potentially diagnostic genes
  - Category C: Genes with limited evidence
  - Category D: No (clinical) evidence for heritable-TAD
  - Recent Genes: Data are recent and preliminary

Renard et al., 2018 J Am Coll

Objectives

- To analyze the clinical efficacy of the ACC/AHA genetic screening guidelines in patients with TAA
- To assess the clinical efficacy of large gene panels including genes classified as not definitively associated with heritable-TAD

Methodology

- All patients 18 and older with diagnosed thoracic aortic aneurysm who underwent genetic testing from August 2012 to September 2023 at a single tertiary medical center
- Two separate testing laboratories
  - Lab A: 35 Gene Panel in 2023
  - Lab B: 52 Gene Panel in 2023
- Study Nomenclature
  - Category A Genes-> “Primary Genes”
  - All Others-> “Secondary Genes”

Table 1. Genes Included in Thoracic Aortic Disease Panels

Both Labs		Lab A	Lab B	
COL3A1	*SMAD4*	*PLOD3*	*ELN*	*GATA6*
FBN1	*SKI*	*ARIH1*	*COL4A5*	*HEY2*
SMAD3	*CBS*	*LTBP3*	*PKD1*	*MIB1*
TGFB2	*BGN*		*PKD2*	*NPR3*
TGFBR1	*FOXE3*		*COL1A1*	*PPP1CB*
TGFBR2	*HCN4*		*COL1A2*	*ROBO4*
ACTA2	*MAT2A*		*EMILIN1*	*SOX18*
MYH11	*MFAP5*		*GATA5*	*TCF7L2*
MYLK	*SMAD2*		*AEBP1*	*TGFBR3*
LOX	*TGFB3*		*GATA4*	*THSD4*
PRKG1	*ADAMTS10*			
EFEMP2	*COL5A1*			
FBN2	*COL5A2*			
FLNA	*MED12*			
NOTCH1	*PLOD1*			
SLC2A10	*SMAD6*			

Legend
Category A
Category B/C
Recent
Category D
Not on List

Patient Characteristics

- 1034 TAA Patients included in study
- Most common criteria for genetic testing was Age Under 60 Years (42.4%)
- No Criteria was present in about a third of patients who underwent genetic testing (30.7%)
- Median number of patients tested for each of the:
  - Primary Genes: 1032 (range: 749-1034)
  - Secondary Genes: 847.5 (range:143-1033)

Table 2. Patient Demographics

Variables	All Patients (N=1034)
Age, years	62 (54-69)
Race	
White	898 (86.9%)
Black	52 (5.0%)
Asian	18 (1.7%)
Other	37 (3.6%)
Unknown	29 (2.8%)
Testing Lab	
A	134 (13.0%)
B	900 (87.0%)
Criteria for Testing*	
Age Under 60 Years	438 (42.4%)
Syndromic Features of CTD	197 (19.1%)
Family History	432 (41.8%)
No Criteria Met	317 (30.7%)

Age is formatted as median (IQR). All other values formatted as n (%).
*Patients may meet more than one criterion and therefore this category does not add up to 100%.
CTD, Connective Tissue Disease; IQR, Interquartile Range.

Results

- Result distributions varied significantly in All Genes and Primary Genes
  - All Genes: Syndromic Features of CTD differed from the three other groups
  - Primary Genes: Syndromic Features of CTD and No Criteria each differed from the three other groups

Table 3. Patient Genetic Testing Results, by testing Criteria and by Gene Groups

Result	Overall (N=1034)	Age Under 60 Years (n=438)	Syndromic Features of CTD (n=197)	Family History (n=432)	No Criteria Met (n=317)	P Value*
All Genes						**<0.001****
Pathogenic	41 (3.97%)	24 (5.48%)	26 (13.20%)	20 (4.63%)	7 (2.21%)	
VUS	282 (27.27%)	112 (25.57%)	50 (25.38%)	127 (29.40%)	87 (27.44%)	
Negative	711 (68.76%)	302 (68.95%)	121 (61.42%)	285 (65.97%)	223 (70.35%)	
Primary Genes (Category A)						**<0.001*****
Pathogenic	34 (3.29%)	24 (5.48%)	25 (12.69%)	19 (4.40%)	2 (0.63%)	
VUS	126 (12.19%)	49 (11.19%)	25 (12.69%)	58 (13.43%)	43 (13.56%)	
Negative	874 (84.53%)	365 (83.33%)	147 (74.62%)	355 (82.18%)	272 (85.80%)	
Secondary Genes (Others)						0.07
Pathogenic	7 (0.68%)	0 (0.00%)	1 (0.51%)	1 (0.23%)	5 (1.58%)	
VUS	181 (17.50%)	70 (15.98%)	28 (14.21%)	83 (19.21%)	53 (16.72%)	
Negative	846 (81.82%)	368 (84.02%)	168 (85.28%)	348 (80.56%)	259 (81.70%)	

* Fisher's exact test was used to compare distribution of genetic results for all four groups. For initially significant results. post hoc analysis using Fisher's exact test and Holm-Bonferroni correction was used.
**Post hoc analysis of the distribution of genetic results for All Genes showed difference between Syndromic Features of CTD and each of the three other groups (all P <0.05).
***Post hoc analysis of the distribution of genetic for the Primary Genes revealed differences between Syndromic Features of CTD and all other groups (all P < 0.05), as well as between Age Under 60 Years and No Criteria groups (P = 0.002) and between Family History and No Criteria (P = 0.016).

Pathogenic Result in Primary Gene by Criteria Combination

- Proportion of pathogenic results in patients with all three criteria or Age Under 60 Years and Syndromic Features of CTD differed significantly from No Criteria (P<0.001)
- Proportion of pathogenic results observed with all other criteria combinations did not differ from proportion with no criteria met

Table 3. Proportion of Pathogenic Results by Combination of Criteria Met

Criteria			Pathogenic Probability**	Sample Size Pathogenic/Total	P Value*
Age Under 60 Years	Syndromic Features of CTD	Family History			
Y	Y	Y	22.00% (12.75%-35.24%)	11/50	**P < 0.001**
Y	Y	N	18.75% (10.19%-31.94%)	9/48	**P < 0.001**
N	Y	N	5.88% (2.02%-15.92%)	3/51	P = 0.123
N	Y	Y	4.17% (1.15%-13.98%)	2/48	P = 0.427
Y	N	Y	1.95% (0.66%-5.57%)	3/154	P = 1
N	N	Y	1.67% (0.57%-4.78%)	3/180	P = 1
N	N	N	0.63% (0.17%-2.27%)	2/317	---
Y	N	N	0.54% (0.09%-2.98%)	1/186	P = 1

* Fisher's exact test comparing each criteria combination to patients who met no criteria.
All P-values adjusted using Holm-Bonferroni. Significant results in bold.
**Presented as percent and 95% Wilson Score confidence intervals.
Y, Yes; N, No.

Limitations

- Retrospective study reliant on medical history documented in electronic medical records
- Mutation interpretations may have changed over time, potentially leading to under estimation of pathogenic mutation rates
- Number of genes tested has changed over time, potentially leading to under estimation of pathogenic mutation rates
- Cost of genetic testing may have introduced a socioeconomic bias in the study population

Conclusions

- Our cohort's genetic mutation rates of 3.97% Pathogenic and 27.27% VUS align with results reported in other studies
- Testing of Secondary Genes yielded little clinically meaningful results
- Pathogenic mutation rates in Primary Genes varied between the three guideline testing criteria, with highest rates in patients with syndromic features of CTD
- Accounting for the combination of criteria met could improve pre-testing risk stratification and influence future guidelines
- High prevalence of VUS across all groups underscores the need for a more nuanced approach for recommendation regarding VUS mutations in clinical practice

Thank You!

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