Precision Medical Care for Thoracic Aortic Disease: Findings from the Montalcino Aortic Consortium

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JOHN RITTER RESEARCH PROGRAM in AORTIC & VASCULAR DISEASE

UTHealth
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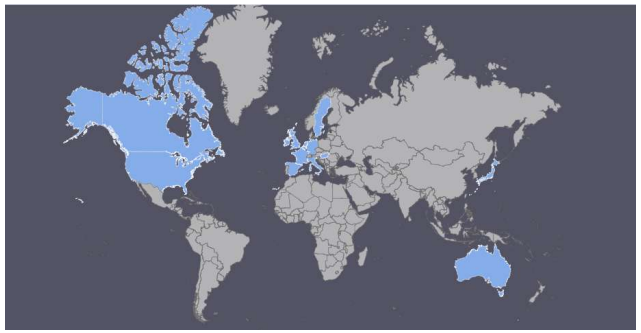
Heritable Thoracic Aortic Disease Genes
"HTAD Genes"

ECM	*FBN1*	fibrillin-1	Marfan syndrome Vascular EDS
	COL3A1	collagen, type III, alpha-1	
	LOX	lysyl oxidase	
TGF-β Signaling	*TGFBR1*	TGF-β receptor type I	Loeys-Dietz Syndrome
	TGFBR2	TGF-β receptor type II	
	SMAD3	SMAD family number 3	
	TGFB2	transforming growth factor β2	
SMC Contraction	*ACTA2*	SM α-actin	
	MYH11	SM myosin heavy chain	
	MYLK	myosin light chain kinase	
	PRKG1	cGMP-dependent kinase I	

Montalcino Aortic Consortium: >30 Aortic Centers Worldwide



<u>Inclusion criteria:</u>
Any individual with a pathogenic or VUS in an HTAD gene

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ACC/AHA Treatment Guidelines 2022: Surgical Thresholds for Loeys Dietz Syndrome

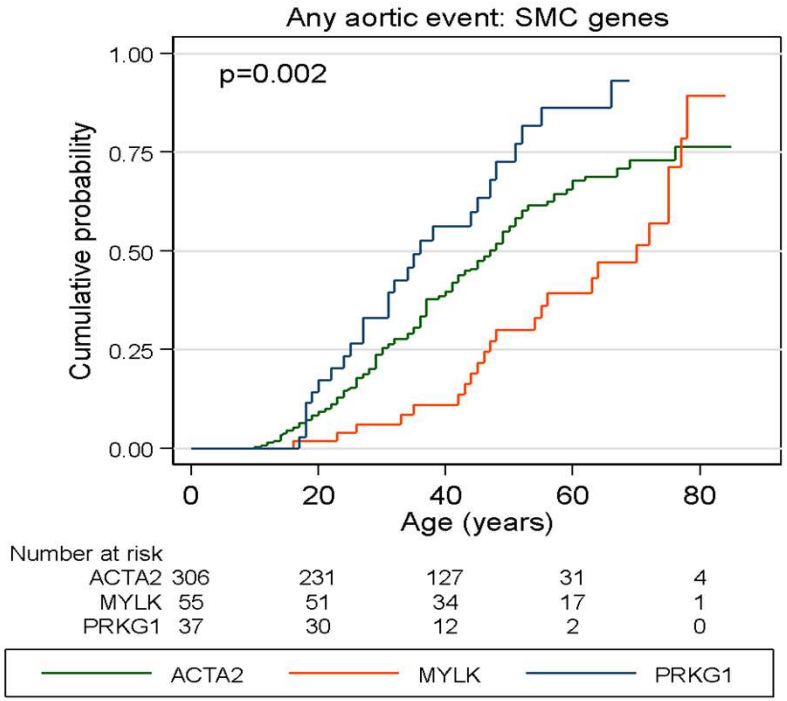
TABLE 11 Surgical Thresholds for Prophylactic Aortic Root and Ascending Aortic Replacement in Loeys-Dietz Syndrome Based on Genetic Variant

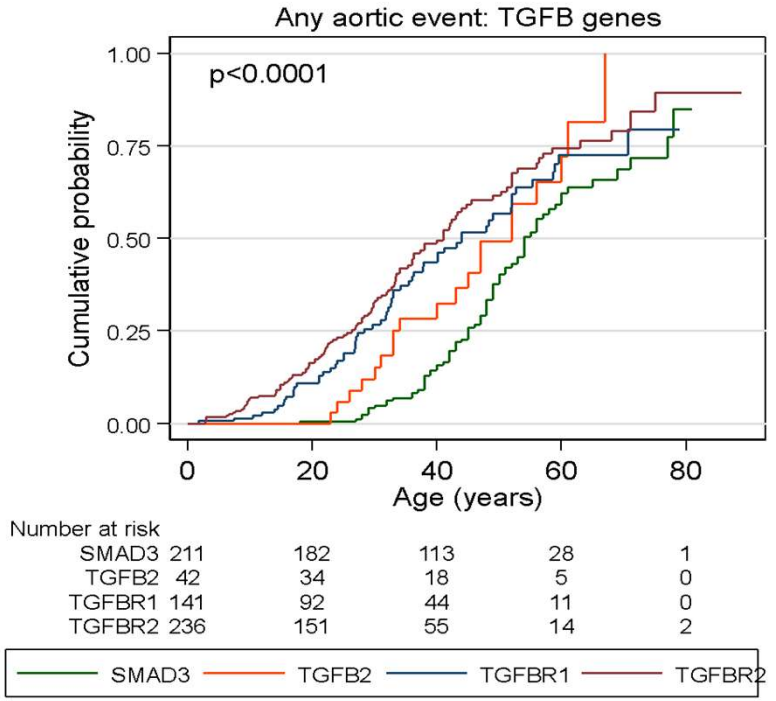
COR	LOE (references)	Genetic Variant	Presence of High-Risk Features*	Aortic Diameter (cm)
1	C-LD[2]	*TGFBR1*	No	≥4.5
1	C-LD[2]	*TGFBR2*	No	≥4.5
2b	C-EO[2]	*TGFBR1*	Yes	≥4.0
2a	C-LD[1,2]	*TGFBR2*	Yes	≥4.0
2a	C-EO[13,16]	*SMAD3*	-	≥4.5†
2b	C-EO[5-7]	*TGFB2*‡	-	≥4.5†
2b	C-EO[9,23]	*TGFB3*	-	≥5.0†

Isselbacher et al. *Circulation* 2022 146(24):e334-e482

Cumulative Risk for an Aortic Event Based on HTAD Gene

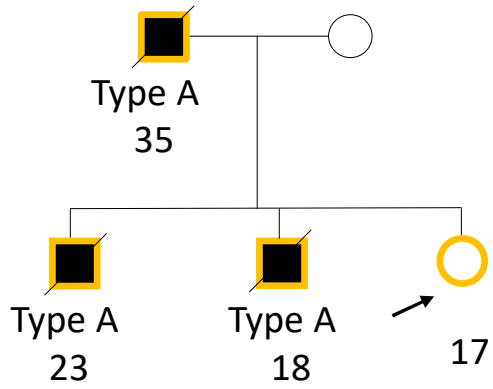
Aortic Event = Surgical repair of an aneurysm, type A, or B dissection





Regalado et al. *JACC* 2022: 857-869

Gene-Based Management:
Repair of a Normal Aorta in a 17 year old



PRKG1

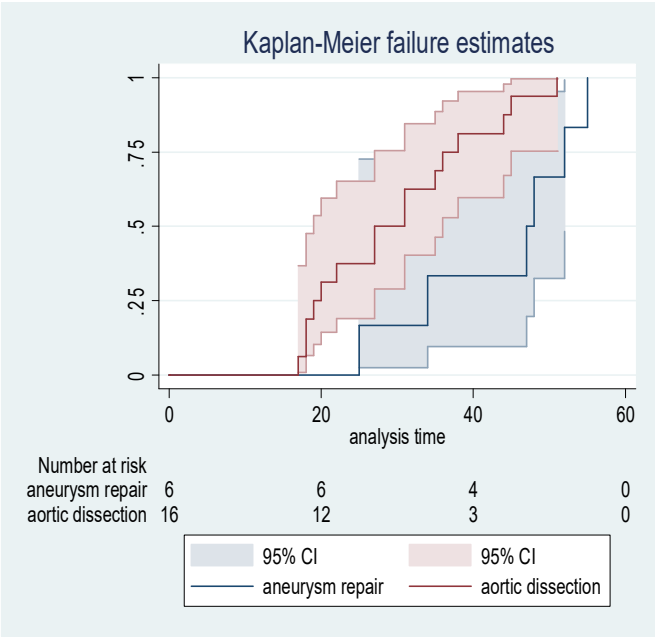


Photo used with permission

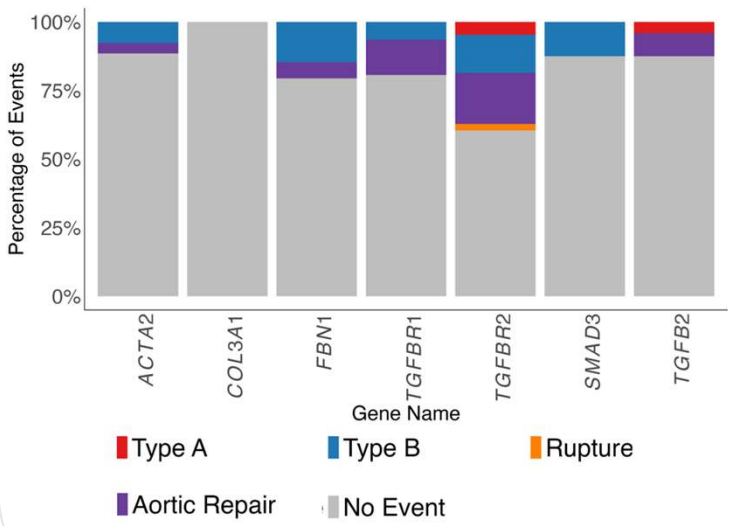
Asari A et al. *J Vasc Cases Innov Tech* 2025 12(2): 102088

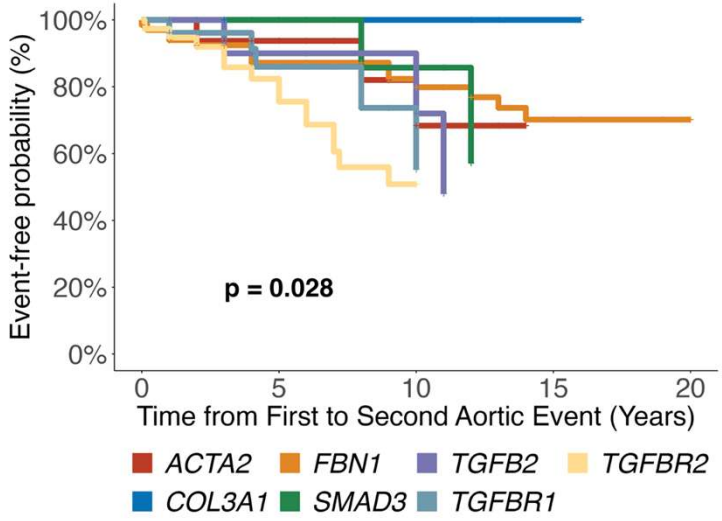
Gene-Specific Risks for Aortic Events After Proximal Aneurysm Repair

Montalcino Aortic Consortium

Elective proximal aneurysm repair
n=229

Second Aortic Events by Gene

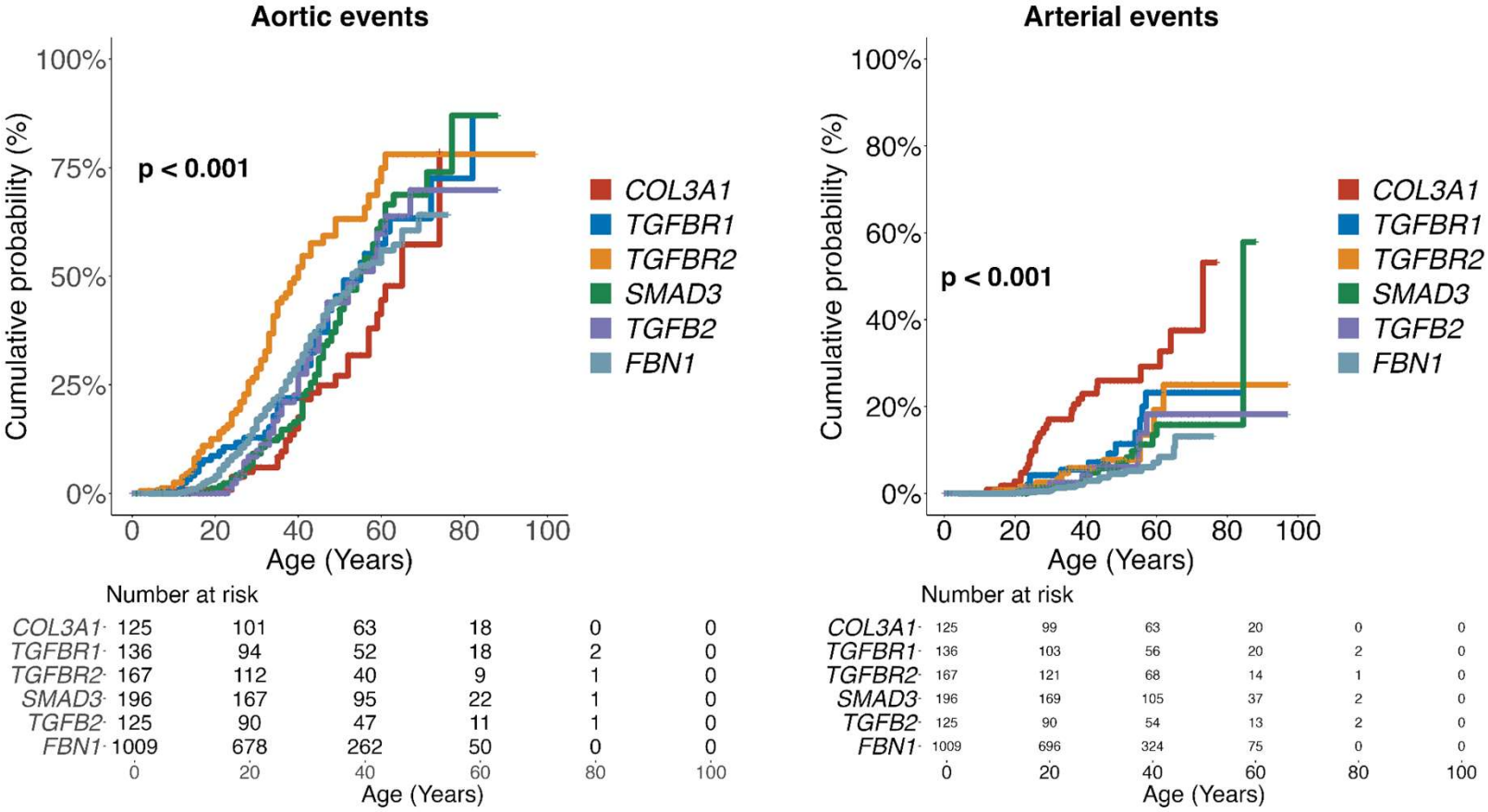




Second aortic events most prevalent in *TGFBR2* cases (40%).

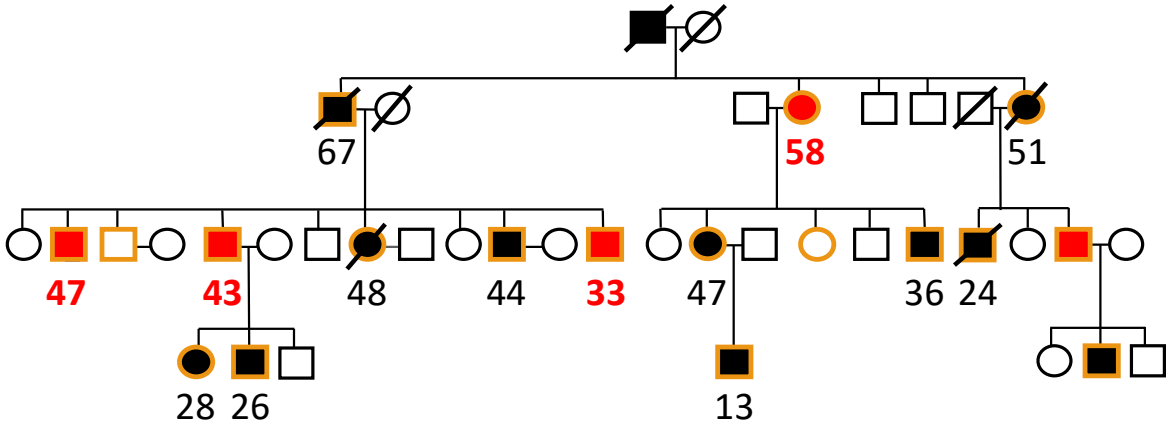
Calderon-Martinez et al., 2026, under revision.

Arterial Versus Aortic Events in VEDS, LDS and MFS: 2864 Cases

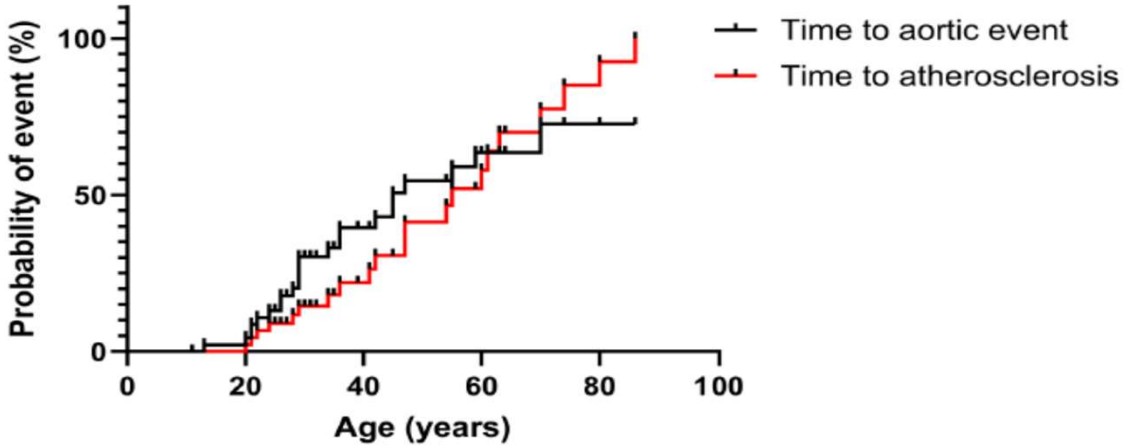


Calderon-Martinez et al., 2025 *JACC* 2355-2367.

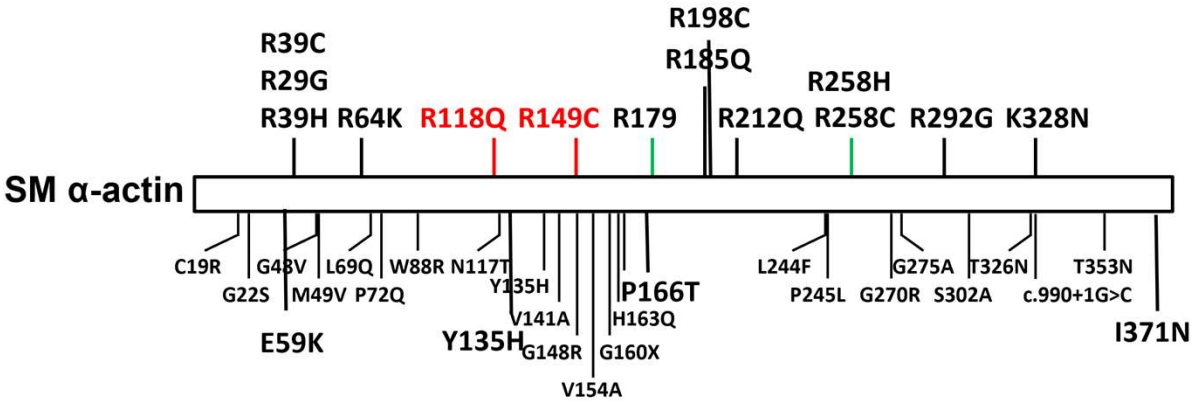
ACTA2 R149C Variant and Early Onset Coronary Artery Disease

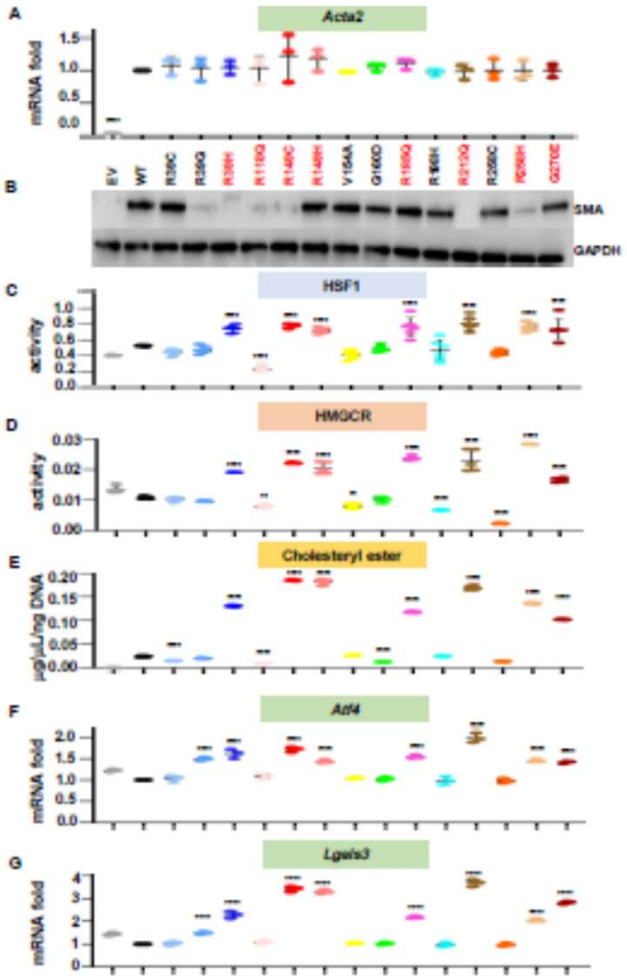


- *ACTA2* R149C
- Thoracic aortic disease
- Early onset coronary artery disease without risk factors



ACTA2 Pathogenic Variants Predisposing to Early Onset Atherosclerosis





Boerio et al, *Circulation Genome Prec Med*, 2026 Feb;19(1):e005169.

Putative Heritable Thoracic Aortic Disease Genes

ECM	***FBN2***	**fibrillin 2**
	MFAP5	**microfibril associated protein 2**
	COL5A1	**collagen, type V, alpha-1**
	COL5A2	**collagen, type V, alpha-2**
	BGN	**biglycan**
	EFEMP2	**EGF-containing fibulin-like extracellular matrix protein 2**
	THSD4	**Adamtsl6**
	EMILIN1	**emilin**
	LTBP3	**latent TGF-β binding protein**
	ELN	**elastin**
TGF-β Signaling	***SKI***	**SKI protooncogene**
	SMAD2	**SMAD family number 2**
	SMAD4	**SMAD family number 4**
	TGFB3	**transforming growth factor, beta-3**
SMC Contraction	***ARIH1***	**ariadne RBR E3 ubiquitin protein ligase 1**
	FLNA	**filamin A**
	MYH9	**myosin, heavy chain 9**
	HCN4	**hyperpolarization-activated cyclic nucleotide-gated potassium channel 4**
Other	***MAT2A***	**methionine adenosyltransferases IIα**
	FOXE3	**forkhead transcript factor E3**
	MTOR	**mechanistic target of rapamycin**
	CBS	**cystathionine beta-synthase**
	NOTCH1	**notch receptor 1**
	SLC2A10	**solute carrier protein 2, member 10**
	IPO8	**importin 8**
	PKD1	**polycystin 1**
	PKD2	**polycystin 2**