SUPPLEMENTAL MATERIAL

Montalcino Aortic Consortium (MAC)

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Supplemental Table 1. Predicted functional impact of 41 *ACTA2* mutations and frequency and age at presentation of aortic events or last follow-up of families and individuals assessed.

Exon	Nucleotide change*	Amino acid substitution†	PolyPhen-2[1]	PROVEAN[2]/ SIFT	Mutation Taster[3]	Mutation Assessor[4]	LRT[5]	FATHMM[6]	# of families assessed	# of individuals assessed	With aortic event		Without aortic event	
											n	Median age (min- max)	n	Median age (min- max)
2	c.55T>C	p.C19R	possibly damaging	Deleterious	disease causing	high	Neutral	Damaging	1	1	1	49	0	
2	c.64G>A	p.G22S	possibly damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	2	1	31	1	68
2	c.115C>T	p.R39C[7-9]	benign	Deleterious	disease causing	medium	Deleterious	Damaging	2	2	2	26 (22- 30)	0	
2	c.115C>G	p.R39G	possibly damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	14	4	29.5 (22- 37)	10	35.5 (1- 65)
2	c.116G>A	p.R39H[10]	benign	Neutral	disease causing	medium	Deleterious	Damaging	2	12	7	37 (23- 76)	5	34 (22- 68)
3	c.143G>T	p.G48V	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	2	1	42	1	49
3	c.145A>G	p.M49V[7, 9]	benign	Neutral	disease causing	medium	Deleterious	Damaging	1	3	1	35	2	11 (8- 14)
3	c.191G>A	p.R64K	benign	Neutral	disease causing	medium	Deleterious	Damaging	1	1	1	49	0	
3	c.206T>A	p.L69Q	probably damaging	Deleterious	disease causing	high	Neutral	Damaging	1	3	3	51 (39- 62)	0	
3	c.215C>A	p.P72Q[10]	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	5	1	47	4	12 (1- 27)
4	c.262T>C	p.W88R	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	10	3	37 (12- 51)	7	55 (21- 62)
4	c.350A>C	p.N117T[11]	possibly damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	4	2	41 (29- 53)	2	62.5 (56- 69)
4	c.353G>A	p.R118Q[11]	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	2	14	8	41 (12- 57)	6	44.5 (24- 80)
5	c.403T>C	p.Y135H[11]	probably damaging	Deleterious	disease causing	medium	Deleterious	Damaging	1	4	1	52	3	48 (35- 53)
5	c.422T>C	p.V141A	possibly damaging	Deleterious	disease causing	medium	Deleterious	Damaging	1	3	1	21	2	34.5 (20- 49)
5	c.442G>A	p.G148R	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	4	4	44.5 (36- 60)	0	
5	c.445C>T	p.R149C[11-13]	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	10	69	33	29 (13- 56)	36	30 (3- 77)
6	c.461T>C	p.V154A[11]	probably damaging	Deleterious	disease causing	medium	Deleterious	Damaging	1	7	2	33.5 (31- 36)	5	25 (13- 73)
6	c.479G>A	p.G160D[10]	probably damaging	Deleterious	disease causing	medium	Deleterious	Damaging	2	9	4	32 (23- 51)	5	54 (1- 85)

6	c.489C>A	p.H163Q	possibly damaging	Deleterious	disease causing	medium	Deleterious	Damaging	1	1	1	41	0	
6	c.496C>A	p.P166T	possibly damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	2	2	39.5 (19- 60)	0	
6	c.535C>T	p.R179C[14]	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	4	4	1	14	3	4 (2- 4)
6	c.536G>A	p.R179H[15-19]	benign	Deleterious	disease causing	medium	Deleterious	Damaging	15	15	6	13 (11- 25)	9	8 (1- 14)
6	c.536G>T	p.R179L[20]	possibly damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	1	0		1	5
6	c.554G>A	p.R185Q[10]	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	2	9	2	54 (41- 67)	7	54 (15- 77)
6	c.592C>T	p.R198C	probably damaging	Deleterious	disease causing	medium	Deleterious	Damaging	2	2	2	22 (12- 32)	0	
6	c.593G>A	p.R198H	benign	Deleterious	disease causing	medium	Deleterious	Damaging	1	3	2	43 (41- 45)	1	33
7	c.635G>A	p.R212Q[10, 12]	probably damaging	Deleterious	disease causing	medium	Deleterious	Damaging	3	16	6	31 (16- 53)	10	17.5 (2- 76)
7	c.732G>T	p.L244F	possibly damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	2	1	14	1	46
7	c.734C>T	p.P245L[10]	possibly damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	1	1	27	0	
7	c.748A>C	p.I250L[10]	possibly damaging	Neutral	disease causing	medium	Deleterious	Damaging	1	1	1	37	0	
7	c.772C>T	p.R258C[11]	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	5	12	6	26 (15- 52)	6	18.5 (5- 63)
7	c.773G>A	p.R258H[11]	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	3	11	9	35 (16- 57)	2	21 (16- 26)
7	c.808G>A	p.G270R	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	1	1	69	0	
8	c.824G>C	p.G275A	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	1	1	43	0	
8	c.874A>G	p.R292G[11]	probably damaging	Deleterious	disease causing	high	Deleterious	Damaging	1	5	3	36 (26- 48)	2	62.5 (53- 72)
8	c.904T>G	p.S302A	possibly damaging	Neutral	disease causing	medium	Deleterious	Damaging	1	4	2	41 (37- 45)	2	18 (1- 35)
8	c.977C>A	p.T326N[10]	benign	Neutral	disease causing	low	Deleterious	Damaging	1	4	0		4	55.5 (35- 75)
8	c.984G>T	p.K328N	possibly damaging	Deleterious	disease causing	medium	Deleterious	Damaging	1	2	2	17	0	
8	c.990+1G>C		NA	NA	disease causing	NA	NA	NA	1	1	1	48	0	
9	c.1058C>A	p.T353N[11]	possibly damaging	Deleterious	disease causing	medium	Deleterious	Damaging	1	10	2	33 (17- 49)	8	31 (9- 72)

*Annotation of cDNA and protein changes are based on the *ACTA2* reference sequence NM_001613.2; †references are cited if the mutation has been previously reported; “n” indicates number of individuals with or without an aortic event; ”min- max” means minimum to maximum age at aortic event; NA means not available.

Supplemental Table 2. Medical histories, aortic disease characteristics and in-hospital treatment and outcomes of 70 *ACTA2* patients who presented for surgical repair due to aneurysm or dissection.

Variable*	**Ascending aortic aneurysm**	**Acute Thoracic Aortic Dissection**			**Chronic Type B dissection**
		Type A	**Type B**	**All**	
n	10	41	10	51	9
Age, years	36.5 (25- 44)	36 (29- 46)	28.5 (21- 41)	36 (27- 46)	21 (16- 26)
Maximum aortic diameter, cm	5.2 (5- 5.5)	5.75 (4.7- 6.75)	4.8		6 (4.1- 6.5)
Aortic disease at other locations					
Ascending aorta	NA	NA	3 (30)		1 (11)
Descending aorta	2 (2)	2 (5)	NA		NA
Abdominal aorta	1 (10)	0	0		0
Presenting symptoms					
Any symptom	4 (40)	38 (97)	10 (100)	48 (98)	8 (100)
Any pain	4 (40)	31 (80)	10 (100)	41 (84)	6 (75)
Chest pain	4 (40)	23 (60)	8 (80)	31 (65)	4 (50)
Back pain	1 (10)	4 (10)	8 (80)	12 (25)	3 (38)
Abdominal pain	0	6 (15)	4 (40)	10 (20)	0
Neck/jaw pain	0	8 (20)	0	8 (16)	0
Upper extremity pain	0	2 (5)	2 (20)	4 (8)	0
Lower extremity pain	0	2 (5)	1 (10)	3 (6)	0
Hypotension	0	5 (13)	0	5 (10)	0
Hypertension	0	3 (8)	4 (40)	7 (14)	0
Congestive heart failure	0	2 (5)	0	2 (4)	0
Dyspnea	3 (30)	8 (20)	1 (10)	9 (18)	1 (12)
Pulse deficit	0	7 (20)	2 (20)	9 (18)	0

Syncope	0	7 (18)	0	7 (14)	0
Vomiting	0	6 (15)	2 (20)	8 (16)	1 (12)
Extremity numbness/weakness	0	3 (8)	4 (40)	7 (14)	0
Edema	0	2 (5)	1 (10)	3 (6)	0
Diarrhea	0	0	1 (10)	1 (2)	1 (12)
Malaise/fatigue	1 (10)	2 (5)	0	2 (4)	0
Neurologic	0	9 (23)	1 (10)	10 (20)	1 (12)
Medical histories					
Bicuspid aortic valve	1 (10)	1 (2)	0	1 (2)	0
Hypertension	1 (10)	9 (23)	3 (30)	12 (24)	3 (33)
Hypercholesterolemia	2 (20)	2 (5)	0	2 (4)	0
Recent pregnancy	0	5 (33)	1 (17)	6 (29)	0
Stroke	1 (10)	2 (5)	0	2 (4)	0
Myocardial infarction	0	2 (5)	0	2 (4)	0
Patent ductus arteriosus	3 (30)	2 (5)	0	2 (4)	0
Mitral valve prolapse	0	1 (3)	0	1 (2)	0
Family history of TAAD	6 (67)	17 (55)	5 (62)	22 (56)	4 (57)
In-hospital treatment					
Composite valve graft root replacement	4 (40)	18 (44)	0		0
Valve-sparing root replacement	5 (50)	2 (5)	0		0
Ascending aortic replacement	1 (10)	17 (42)	0		0
Aortic arch replacement (partial)	1 (10)	8 (20)	0		0
Aortic arch replacement (total)	2 (20)	4 (10)	0		0
Descending aorta replacement	0	0	2 (20)		1 (11)
Extent I TAAA repair	0	0	0		7 (78)
Extent II TAAA repair	0	0	0		1 (11)
Aorto-bifemoral bypass	0	0	1 (10)		0

Endovascular repair	0	0	3 (30)		0
Medical therapy	0	0	4 (40)		0
Peri-operative complications					
Tamponade	1 (10)	7 (34)	0	7 (16)	0
Myocardial infarction	0	3 (9)	0	3 (7)	0
Neurological deficit	0	3 (34)	0	3 (7)	1 (17)
Limb ischemia	0	2 (6)	1 (11)	3 (7)	1 (17)
Renal failure	0	6 (18)	1 (11)	7 (16)	0
Mesenteric ischemia	0	0	0	0	3 (33)
Atrial fibrillation	1 (11)	5 (15)	0	5 (12)	1 (17)
# days hospitalized	6 (5- 9)	10 (8- 18)	12 (9- 23)	11 (8- 18)	19 (14- 38)
In-hospital deaths	0	6 (15)	1 (10)	7 (14)	0

*Categorical variables are presented as # of individuals and percentage in parenthesis (missing values were excluded in calculations) and continuous variables are presented as median (interquartile range); NA- not applicable.

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