TGFB2 loss of function mutations cause familial thoracic aortic aneurysms and acute aortic dissections associated with mild systemic features of the Marfan syndrome

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ESP Cohorts

Acute Lung Injury (ALI), Atherosclerosis Risk in Communities (ARIC), Cardiovascular Health Study (CHS), Chronic Obstructive Pulmonary Disease (COPDGene), Coronary Artery Risk Development in Young Adults (CARDIA), Cystic Fibrosis (CF), Early Pseudomonas Infection Control (EPIC), Framingham Heart Study (FHS), Jackson Heart Study (JHS), Lung Health Study (LHS), Multi-Ethnic Study of Atherosclerosis (MESA), Pulmonary Arterial Hypertension (PAH), Severe Asthma Research Program (SARP), Women's Health Initiative (WHI)

Supplementary note

Family Recruitment, Characterization, and Sample Collection

For the Houston cohort, the study protocol was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston, and the study participants gave informed consent to participate in these studies. Families with two or more members affected with TAAD were enrolled into the study. Phenotypic characterization of vascular diseases, including TAAD and ICAs, was previously described[1]. Specifically in this paper, individuals with aortic root measurements and Z scores over 2.0 were scored as positive[2]. Blood or saliva samples were obtained from affected individuals and family members. Surgical aortic and/or skin biopsy tissue were also obtained from affected members when possible. Medical records, including imaging studies of the aorta and cerebral vessels, surgical reports, hospital records, and physicians' notes, were reviewed. Phenotypic features beyond the vascular system, including features of Marfan syndrome and Loeys-Dietz syndrome, were assessed in *TGFB2* mutation carriers examined by a clinical geneticist (DMM)[3, 4]. Tissue was harvested and SMCs explanted as previously described[5, 6]. Control aortic tissue was obtained from the International Institute for the Advancement of Medicine from individuals who died of non-vascular disease and age- and gender-matched to the patients as closely as possible (n = 2).

French probands and families were recruited through the National Reference Center for Marfan syndrome and related disorders and through related centers nationwide. All patients were screened for diagnosis of possible syndromic (notably MFS) or non syndromic TAAD through a multidisciplinary clinic including systematic slit-lamp examination and extensive imaging. Blood samples were obtained from patients in agreement with the French Bioethic laws and genomic DNA prepared as previously reported[7].

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Supplementary Table 1 Rare nonsynonymous, nonsense, and indel variants identified by exome sequencing that are segregated with diseases in families

Gene	Location	TAAD family ID	Nucleotide change	aminoAcids	polyPhen	Present in controls[a]
TGFB2	chr1:218610772	TAA288	GTACAA/G	p.Tyr341Cysfs*25[d]	NA	0/3795[b]
FAM5C	chr1:190068100	TAA288	A/G	Leu450Pro	benign	0/1525
DISP1	chr1:223177116	TAA288	G/A	Val793Met	probably-damaging	1/1536
ZNF488	chr10:48370770	TAA288	C/G	Pro80Ala	probably-damaging	0/1329
COL4A2	chr13:111156311	TAA288	T/C	Met1419Thr	probably-damaging	3/1157
UIMC1	chr5:176332446	TAA288	T/G	Gln666Pro	probably-damaging	3/1537
BDP1	chr5:70798515	TAA288	C/T	Pro713Leu	probably-damaging	1/1537
GPT	chr8:145730072	TAA288	G/A	Arg83His	probably-damaging	0/1534
STK32A	chr5:146741152	TAA288	C/T	Thr212Met	possibly-damaging	0/1529
LPIN2	chr18:2922148	TAA288	C/T	Asp742Asn	possibly damaging	0/1490
COL4A2	chr13:111121570	TAA288	A/G	Lys701Arg	benign	3/1537
DGCR8	chr22:20073742	TAA288	C/A	Leu86Ile	benign	2/1537
NIPAL4	chr5:156899672	TAA288	G/A	Val369Ile	benign	1/1537
FAM83H	chr8:144812521	TAA288	G/A	Pro78Ser	benign	0/1537
CABYR	chr18:21736772	TAA288	C/G	Ser436Cys	NA	1/1535
DYTN	chr2:207527977	TAA288	T/TCC	p.Glu428Glyfs*59	NA	7/1537
TGFB2	chr1:218607723	MS239	C/A	C229X	NA	0/10750 (EVS)[c]
PARP4	chr13:25021200	MS239	C/T	L1080F	benign	0/10752 (EVS)
USP32	chr17:58288396	MS239	A/G	N801S	benign	680/10680 (EVS)
NBPF10	chr1:145298168	MS239	A/G	A194T	possibly damaging	0/3230 (EVS)
TMEM206	chr1:212560248	MS239	C/T	R171C	possibly damaging	15/10758 (EVS)

[a]Rare variants present in the number of control chromosomes. [b]Control data were obtained from in-house 1500 exome data set. [c]Control data were obtained from the EVS database (http://evs.gs.washington.edu/EVS/). [d] the only exome rare variant identified in family TAA288 that segregated with thoracic aortic aneurysms and aortic dissections when additional affected family members were assessed.

Supplementary Table 2 Primers used for *TGFB2* sequencing and mRNA quantification

Primers	Primer sequence (5' → 3')
RT-PCR forward primer	TCGAGGACCTGACACGAGGGTGGAAATGGATACACGA
RT-PCR reward primer	GGAGAAGCAGATGCTTCTGG
Exon 1 forward primer	CCAAACAACTCTCCTTGATCTA
Exon 2 forward primer	CCCTTATGGTTTCTTGGGAT
Exon 3 forward primer	GTGACCATGCAATTGAGATG
Exon 4 forward primer	GAATGGCTTCACCATAAAGG
Exon 5 forward primer	CAGCTGATGCTGCTTTGGTG
Exon 6 forward primer	CACTTGAGATTACAATAAAGCC
Exon 7 forward primer	GCCTACTCAGTGCTGTGAC
Exon 1 reward primer	AAGGGCGATCCCGGGAGCTG
Exon 2 reward primer	GTTCAAGGTTGCAGTGAGCT
Exon 3 reward primer	CAAGTTTTGGTTACCTGC
Exon 4 reward primer	CAACCATATCACTGTCCAAATG
Exon 5 reward primer	TGCACTCTATCTGGCCTT
Exon 6 reward primer	CCAGTACCCATACATGTG
Exon 7 reward primer	ACTGATGAACCAAGGCTCT

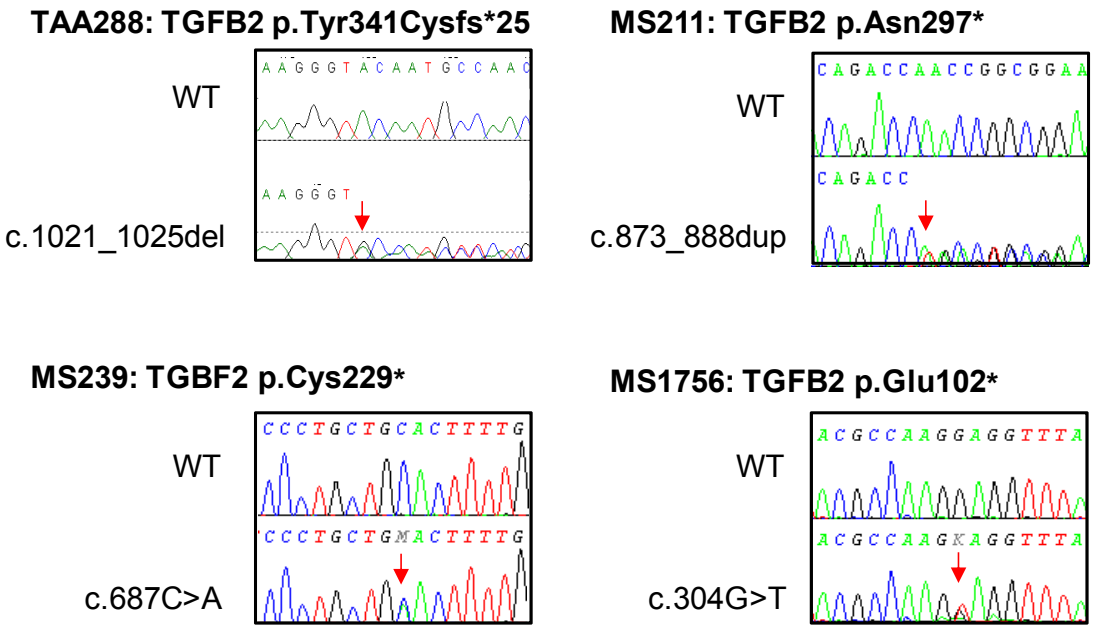
Supplementary Table 3 Clinical data of individuals with *TGFB2* mutations

	TAA288											MS239						MS1758	MS211
Features	III:2	III:3	III:4	III:5	III:8	III:9	III:11	III:12	IV:1	IV:2	IV:3	III:16	IV:2	IV:12	IV:20	IV:22	V:5	II:8	III:14
Sex	F	M	F	M	F	M	M	M	M	M	M	M	M	F	F	M	M	M	M
Age (years)	50	d.41	46	47	32	43	42	39	22	18	10	59	56	41	39	27	17	50	33
Ht (cm)	178	191	168	173	173	198	190	201	180	185	157	182	190	182	175	179	187	165	179
Wt (kg)	64	84	105	71	55	122	94	89	67	73	44	84	90	82	57	60	89	60	75
Age at diagnosis (years)		41		40	25	36	35	32	18	17	5	53	45	36	32	27		47	31
Age at surgery (years)							35					60	43					47	31
Reason for surgery							TAA					TAA	MVP					TAD	TAD
Annulus (cm)	.	.	Nl*	.	.	.	.	.	.	.	.	2.6	2.8	2.5	2.2	2.4	2.4		
Valsalva (cm)	2.6	8*	Nl*	4.7	3.4-3.5	4.7 (CT)	5.4 (CT)	4.1	4.1	3.4	2.9	5	4.8	4.1	4.6	3.6	3.7		
Sinotubular junction (cm)	.	.	Nl*	.	.	.	.	.	.	.	2.0	3.4	3.5	3.2	2.6	2.6	3		
Ascending aorta (cm)	.	.	Nl*	.	.	.	.	.	.	.	1.7	3.5	3.5	3.2	2.3	2.5	2.8		
Z score, sinuses of Valsalva	.	.	.	.	2.7	.	.	.	5.1	2.4	2.1	4.2	3.4	2.24	7.2	2.75	1.3		
LVEDD (cm)	.	.	.	.	.	.	.	.	.	.	.	5.7	5.4	6.0	4.7	5.0	6.1	4.9	5.9
Arterial tortuosity	.	.	.	.	no	.	.	.	.	.	.	yes	yes	.	.	.	.	yes	no
Intracranial aneurysm	no	.	no	.	no	.	.	.	no	no	.	no	no.	.	.	.	.	.	.
Other cardiac disease		DCM							MVP	MVP			MVP						
Pectus deformity	no	.	.	.	no	no	mild	mild	no	no	mild	mild	yes	no	yes	no	no	yes	no
Arm span to height ratio	0.93	.	.	.	1.02	.	1.03	.	0.94	1.02	0.99	1.02	1.07	1.04	0.96	1.01	1.01	1.04	1.02
Wrist sign	no	.	.	.	yes	.	yes	.	no	no	.	no	no	yes	yes	no	no	yes	yes
Thumb sign	no	.	.	.	no	.	yes	.	no	yes	.	no	yes	yes	yes	no	no	yes	yes
Spondylolisthesis	.	.	.	.	.	.	.	.	.	.	.	no	yes	no	no	no	no	no	.
Scoliosis	yes	.	.	.	yes	.	no	no	mild	no	no	no	no	mild	no	no	no	no	no
Flat feet	yes	.	.	.	no	.	yes	yes	yes	yes	no	yes	yes	no	yes	yes	yes	yes	no
Protrusio acetabularis	.	.	.	.	.	.	.	.	.	.	.	no	yes	no	no	no	no	no	no
Joint hyperflexibility	yes	.	.	.	yes	.	no	yes	yes	yes	no	no	no	yes	yes	no	yes	yes	yes
High arched palate	yes	.	.	.	yes	.	no	yes	yes	yes	yes	yes	yes	no	yes	no	no	no	no
Striae atrophicae	no	.	.	.	no	.	yes	yes	yes	yes	no	yes	yes	no	no	yes	yes	no	no

Operated hernia	no	yes	.	yes	no	.	yes	no	yes	no	no	no	no	yes	no	no	no	no	yes
Cutis laxa	no				no				no	no	no	no	no	no	no	no	no	no	no
Pneumothorax	no	.	.	no	no	no	no	no	no	no	no	no	no	yes	no	no	no	no	no
Dural ectasia	.	.	.	.	.	.	.	.	.	.	.	no	yes	yes	.	no	.	yes	.
Emphysema	no	no	.	no	no	no	no	no	no	no	no	no	yes	.	.	.	.	yes	.
Phlebitis	no	no	.	no	no	no	no	no	no	no	no	yes	yes	no	no	no	no	no	no
Lens dislocation	no	.	.	.	no	.	.	.	no	no	no	no	no	no	no	no	minor†	no	no
Flat cornea	.	.	.	.	.	.	.	.	.	.	.	no	yes	no	no	no	yes	no	no
Dolichocephaly	no	.	.	.	no	.	.	.	no	no	no	no	no	no	no	no	no	no	no
Malar hypoplasia	no	.	.	.	no	.	.	.	no	no	no	no	no	no	no	no	no	no	no
Down-slanting palpebral fissures	no	.	.	.	no	.	.	.	no	no	no	no	no	no	no	no	no	no	no
Retrognathia	no	.	.	.	no	.	.	.	no	yes	no	no	no	yes	no	no	no	no	no
Enophthalmos	no	.	.	.	no	.	.	.	no	no	no	no	no	no	no	no	no	no	no
Hypertelorism	no	.	.	.	no	.	.	.	no	no	no	no	no	no	no	no	no	no	no
Cleft palate or abnormal uvula	no	.	.	.	no	.	.	.	no	no	no	no	no	no	no	no	no	no	no
Craniosynostosis	no	.	.	.	no	.	.	.	no	no	no	no	no	no	no	no	no	no	no

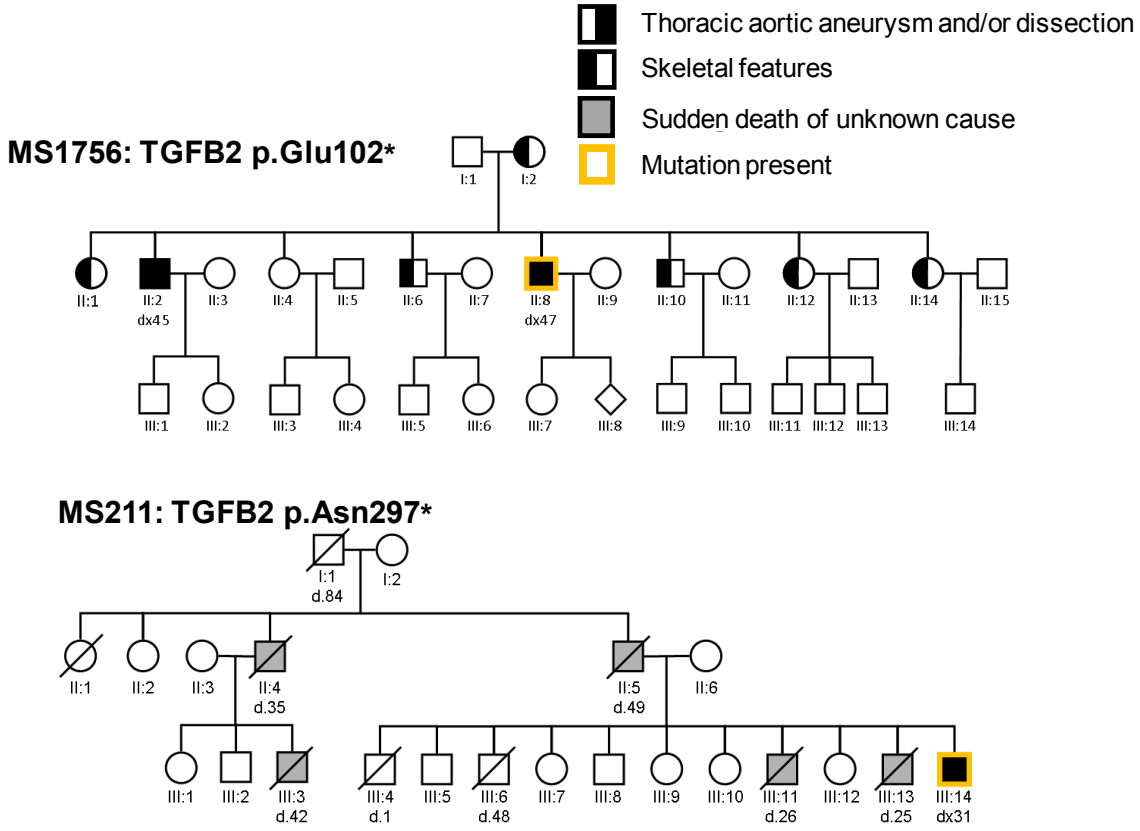
Ht : height; Wt: weight; TAA: thoracic aortic aneurysm; TAD: thoracic aortic dissection; "." : data not available; "*" : verbal report; blank: not applicable; Nl : normal; aortic measurements were obtained by echocardiography unless otherwise noted; MR: obtained by MR imaging; CT: obtained by CT imaging;; DCM: dilated cardiomyopathy; MVP: mitral valve prolapse; †individual noted as having minor ectopia lentis by French ophthalmologists, which is not recognized as lens dislocation in the USA.

Supplementary Figure 1



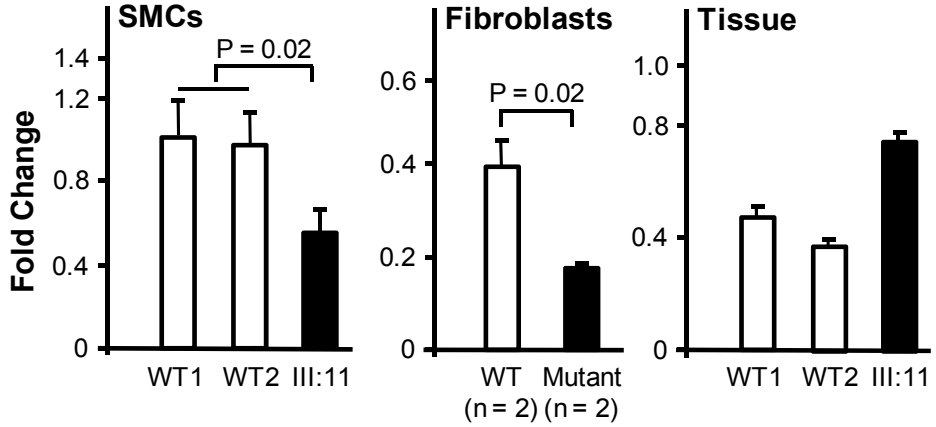
Supplementary Figure 1. Sequencing chromatograms showing the *TGFB2* mutations identified in the four families that all result in a premature termination codon (two missense mutations and a frameshift deletion and duplication).

Supplementary Figure 2



Supplementary Figure 2. Pedigrees of the two additional families with *TGFB2* mutations p.Asn297* (MS1756) and p.Glu102* (MS211) identified in the probands. Black-filled symbols indicate a finding of aortic root aneurysm and/or dissection, gray-filled symbols indicate sudden death due to an unknown cause, and half-filled symbols indicate individuals with skeletal features. Open symbols indicate individuals with a normal or unknown phenotype**.** The age at diagnosis of aortic root enlargement and/or dissection ("dx") is shown in years and "d" indicates the age at death.

Supplementary Figure 3



Supplementary Figure 3. Densitometry analysis of immunoblots for the TGF-β2 proprotein shown in the Figure 2c and 3c. Quantification of the immunoblots confirms decreased accumulation of TGF-β2 proprotein in cultured SMCs and fibroblasts, but increased expression of TGF-β2 proprotein in whole aortic tissue. P values represent statistical differences calculated from quantification of multiple immunoblots.