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Supplemental Data

Rare Copy Number Variants Disrupt Genes Regulating Vascular Smooth Muscle Cell Adhesion and Contractility in Sporadic Thoracic Aortic Aneurysms and Dissections

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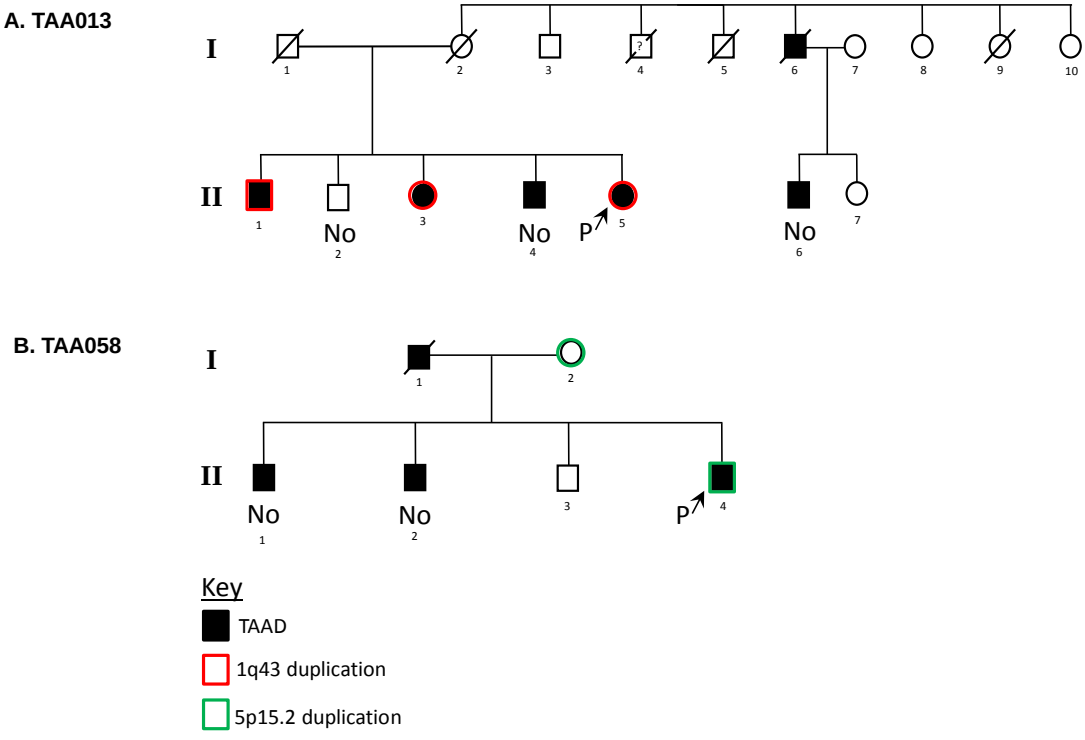
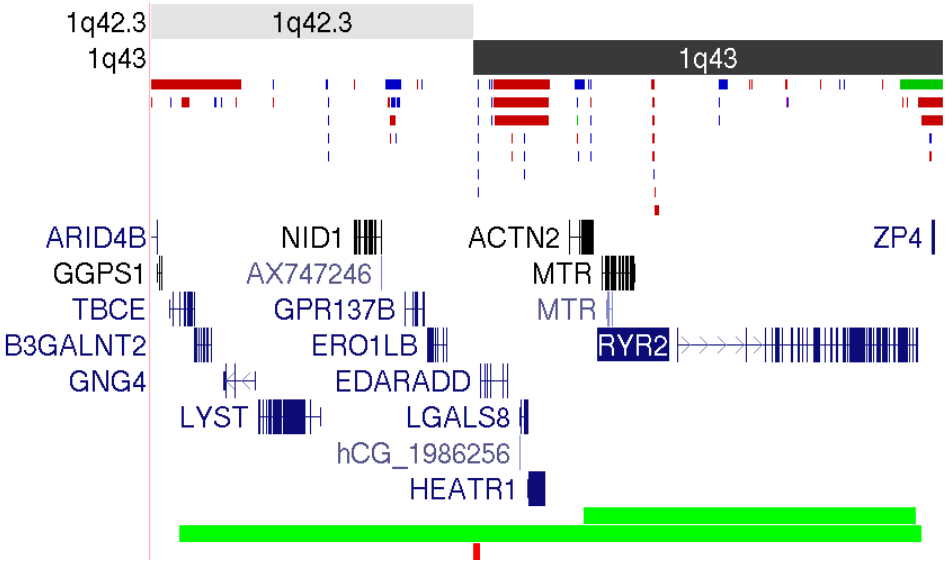
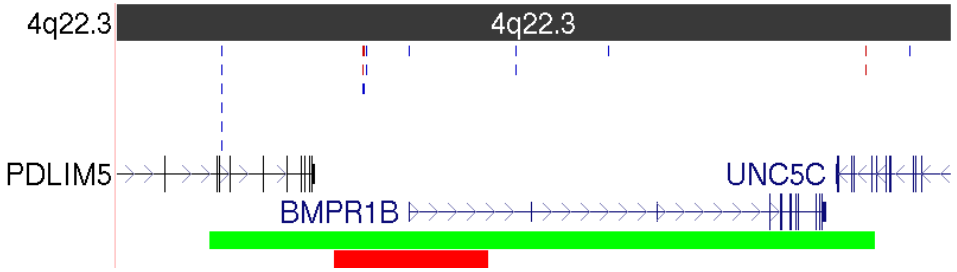


Figure S1. Rare CNVs Are Inherited but Do Not Segregate with FTAAD in Two Pedigrees
Circles indicate females; squares indicate males; the legend indicates affected status and the presence or absence of CNVs in family members; individuals who were confirmed not to harbor the CNV are labeled "No".
(A) In family TAA013, a 340 Kb duplication involving six genes in 1q43 (coordinates 239561201-239903600) is not present in two affected relatives (II-4 and II-6) of the proband (II-5, indicated by the letter P with arrow).
(B) In family TAA058, a 250 Kb duplication involving the *DAP* gene in 5p15.2 (coordinates 10763247-11011635) is present in the unaffected mother (I-2) of the proband (II-4).

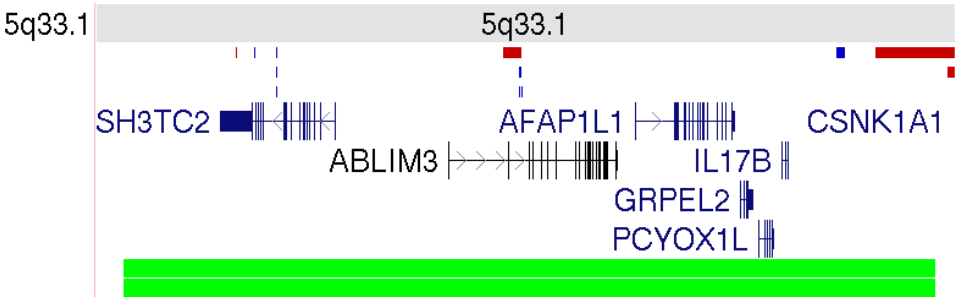
A.


1q42.3
1q42.3
1q43
1q43
ARID4B
NID1
ACTN2
ZP4
GGPS1
AX747246
MTR
TBCE
GPR137B
MTR
B3GALNT2
ERO1LB
RYR2
GNG4
EDARADD
LYST
LGALS8
hCG_1986256
HEATR1

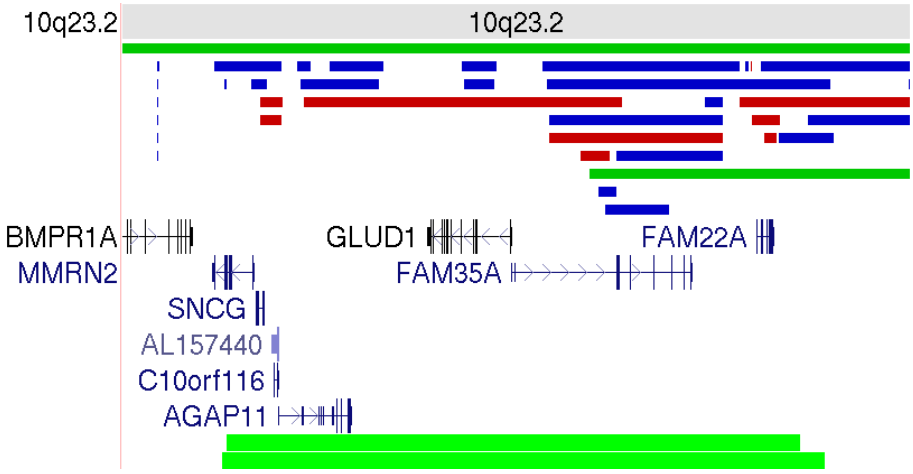
B.


4q22.3
4q22.3
PDLIM5
UNC5C
BMPR1B

C.


5q33.1
5q33.1
SH3TC2
AFAP1L1
CSNK1A1
ABLIM3
IL17B
GRPEL2
PCYOX1L

D.



E.

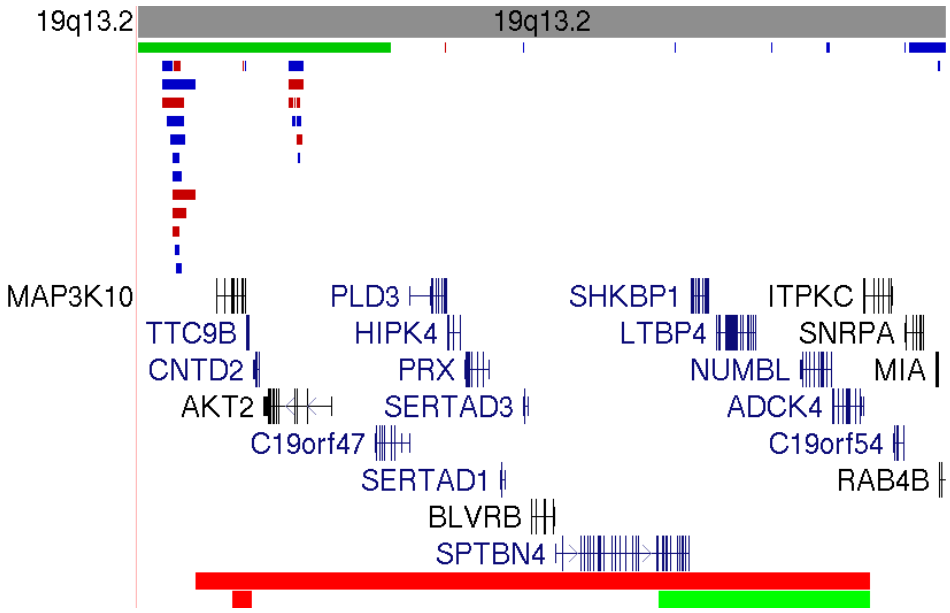


Figure S2. Five Large, Rare and Recurrent CNV Regions in TAAD Cases as Illustrated in the UCSC Genome Browser

Chromosomal coordinates are in base pairs. CNVs in TAAD cases (labelled as TAAD) and in unaffected individuals in the Database of Genomic Variants (labelled as DGV) are shown as red bars (deletions), green bars (duplications) or blue bars (deletions and duplications).
(A) Two duplications involving a common 1 Mb region of 1q43 with three genes;
(B) two duplications and one deletion involving the *BMPR1B* gene in 4q22.3;
(C) two duplications involving six genes in 5q33.1;
(D) two duplications involving seven genes in 10q23.2;
(E) one duplication and one deletion involving six genes in 19q13.2.

Table S1. Control and TAAD Datasets Used for Association Tests

Dataset	dbGAP Accession	Platform	Original	Selected	Filtered	CNVs	Cutoff
Study of Addiction: Genetics and Environment (SAGE)	phs000092.v1.p1	1M	3847	1152	1092	70	150
National Institute of Neurological Disorders and Stroke (NINDS) Repository Neurologically Normal Control Collection	phs000004.v1.p1	370D	2723	848	816	37	73
Whole Genome Association Twin Study of Myopia and Glaucoma Risk Factors	phs000142.v1.p1	610Q	2994	1802	1783	43	160
A Genome Wide Scan of Lung Cancer and Smoking	phs000093.v2.p2	550HH	1629	827	791	25	125
Age related Macular Degeneration (AMD)--Michigan, Mayo, AREDS, Pennsylvania (MMAP) Cohort Study: A Joint Genome Wide Association Study	phs000182.v1.p1	370Q	1545	459	440	44	94
TOTAL CONTROLS			**12738**	**5088**	**4922**		
STAAD BCM		370Q		418	392	45	140
STAAD UTHSC		370Q		387	366	40	140
FTAAD		660W		122	87*	16	68
TOTAL TAAD				**927**	**856**		

Platform: Illumina Beadchips used for each dataset (1M:1M-Duo, 370D:CNV370-Duo, 610Q: 610-Quad; 550HH: HumanHap-550K; 370Q: CNV370-Quad, 660W: 660-Quad); Original: Total number of genotypes in each dataset available for general research use; Selected: Subset of genotypes selected for analysis; Filtered: Remaining genotypes after quality control; CNVs: average number of CNVs per individual in each dataset; Cutoff: individuals with more CNV calls were excluded from further analysis.

Table S2. Rare CNV Regions in UTHSCH TAAD Patients

Chr	Start	Length	Gene(s)	Copy	Cases	Controls
2	54131764	2002168	*C2ORF73*,*ACYP2*,*SPTBN1*[a],*RTN4*[d],*RPS27A*,*MTIF2*,*CCDC104*,*SMEK2*, *PNPT1*,*EFEMP1*,*CCDC88A*	Gain[b]	2	0
5	78387268	116492	*BHMT*,*BHMT2*,*DMGDH*	Gain[b]	2	2
10	81660001	350548	*SFTPD*,*C10ORF57*,*PLAC9*,*ANXA11*	Gain/Loss[b]	2	2
16	14929488	1509330	***MYH11***,*ABCC6*,*NOMO2*,*NDE1*,*ABCC1*,*MPV17L*,*C16ORF45*,*C16ORF63*, *KIAA0430*, *NTAN1*	Gain[c]	7(B,F)	5
1	11697543	284456	*AGTRAP*,*MTHFR*,*CLCN6*[d],*NPPA*[d],*NPPB*[d],*PLOD1*[d],*MFN2*[a],*TNFRSF8*, *TNFRSF1B*,*PRDM2*	Gain	1	0
1	71194152	119439	*PTGER3*[a],*ZRANB2*[a]	Gain	1	0
1	176939550	127554	*RALGPS2*[a]	Gain	1	0
1	233605643	287563	*GNG4*,*LYST*[a]	Gain	1	1
1	235967993	109591	*RYR2*[a]	Gain	1	1
2	238637566	165432	*ILKAP*,*KLHL30*,*ESPNL*,*SCLY*[a]	Gain	1	0
3	65485437	965991	*MAGI1*[a],*SLC25A26*[a]	Gain	1	1
4	65791505	158105	*EPHA5*	Loss	1	0
4	95973863	372128	*BMPR1B*,*PDLIM5*[a]	Gain	1(B)	0
4	159268470	552656	*RXFP1*[d],*C4orf18*,*TMEM144*,*ETFDH*[a]	Gain	1	0
4	165729934	413958	*TRIM61*	Gain	1	1
5	37537353	358478	*GDNF*,*WDR70*[a,d]	Gain	1	0
5	72435947	579062	*RGNEF*[a],*FOXD1*,*BTF3*,*UTP15*,*ANKRA2*,*TMEM171*,*TMEM174*	Gain	1	0
5	76205711	548115	*PDE8B*[a],***AGGF1***,*CRHBP*,*ZBED3*,*S100Z*[a]	Gain	1	0
5	79048094	591370	*THBS4*,*CMYA5*,*SERINC5*[d],*MTX3*	Loss	1	1
5	142058254	631925	*ARHGAP26*,*NR3C1*[a],*FGF1*[a]	Gain	1	0
5	148274871	566620	*ABLIM3*,*AFAP1L1*,*SH3TC2*,*HTR4*,*GRPEL2*,*PCYOX1L*,*IL17B*	Gain	1(B)	0
6	45050278	439793	*SUPT3H*	Loss	1	0
6	82862011	286885	*IBTK*,*TPBG*	Gain	1	0
6	105720900	659049	*PREP*[d], *POPDC3*	Loss	1	0
6	151566770	522945	*AKAP12*[d],*ZBTB2*,*RMND1*[d],*C6ORF211*[d],*C6ORF97*[d],*ESR1*[a]	Gain	1	1
7	11164718	277626	*THSD7A*[a], *PHF14*[a]	Gain	1	0
7	33820265	168561	*BMPER*[a]	Gain	1	1

7	94753911	24612	*PON1*[a],*PPP1R9A*[a]	Gain	1	0
8	87256311	201843	*WWP1*[a]	Gain	1	1
8	106724085	733759	***FOG2***[a]	Gain	1	0
9	3360161	1478714	*RFX3*[a],*PPAPDC2*[d],*C9ORF68*[d],*CDC37L1*[d],*AK3*,*RCL1*[a]	Gain	1	0
9	70696280	646370	*PIP5K1B*[d],*FXN*[d],*TJP2*[d],*C9ORF61*	Gain	1	1
9	116808501	244161	*TNC*,*DEC1*	Loss	1	0
10	88690618	321450	*EMILIN3*[a],*SNCG*,*AGAP11*,*C10ORF116*,*GLUD1*	Gain	1	0
11	3585600	108374	*NUP98*[a],*ART1*,*ART5*,*CHRNA10*	Gain	1	0
11	44771655	106204	*TSPAN1*	Loss	1	1
11	133512319	609098	*JAM3*[a],*NCAPD3*,*ACAD8*,*B3GAT1*,*GLB1L2*[d],*GLB1L3*[d],*VPS26B*,*THYN1*	Gain	1	0
12	27112222	567519	*PPFIBP1*,*STK38L*,*ARNTL2*	Gain	1	1
12	123719029	242979	*SCARB1*	Gain	1	1
13	19275448	452134	*ZMYM2*,*GJA3*[d],*GJB2*[d]	Gain	1	0
13	24172526	262493	*CENPJ*, *RNF17*[a]	Gain	1	0
15	37439530	440597	*THBS1*,*FSIP1*	Gain	1	0
15	97611698	460871	*MEF2A*[a],*LRRC28*[a,d]	Gain	1	0
16	76251592	147425	*VAT1L*,*NUDT7*	Loss	1	0
16	83156705	51323	*COTL1*,*WFDC1*,*KCNG4*,*LRRC50*,*HSDL1*,*TAF1C*,*MBTPS1*,*SLC38A8*,*NECAB2*, *ATP2C2*[d],*OSGIN1*,*HSBP1*,*MLYCD*,*ADAD2*,*CDH13*[d]	Loss	1	0
17	14045669	1353365	*COX10*[a],*CDRT15*,*HS3ST3B1*,*PMP22*,*TEKT3*,*CDRT4*[a]	Loss	1(B)	1
17	75450416	147025	*TBC1D16*[a]	Gain	1	0
18	27738638	270504	*RNF125*,*RNF138*,*KIAA1012*[a]	Gain	1	0
18	42827852	345178	*IER3IP1*,*CORL2*,*HDHD2*	Loss	1	0
19	45748633	171836	*SPTBN4*[a],*SHKBP1*,*LTBP4*,*NUMBL*,*ADCK4*,*ITPKC*[a]	Gain	1(B)	0
20	2695481	255546	*PTPRA*[a],*C20ORF141*,*FAM113A*,*VPS16*,*CPXM1*	Gain	1	0
20	3732593	93445	*CDC25B*[a],*C20ORF29*,*PANK2*[a],*VISA*	Gain	1	0
20	17941461	184763	*CSRP2BP*,*OVOL2*	Gain	1	0
21	45574146	126365	*COL18A1*[a]	Gain	1	0
X	134217460	448164	*ZNF75D*,*ZNF449*,*DDX26B*	Gain	1	1
X	152323546	309812	*TREX2*,*DUSP9*,*BGN*,*UCH5IP*,*ATP2B3*,*FAM58A*,*PNCK*,*SLC6A*,*BCAP31*[a]	Gain	1	0
X	153846405	363482	*F8*[a],*FUNDC2*,*MTCP1*,*BRCC3*,*VBP1*,*RAB39B*,*CLIC2*[d]	Gain	1	0

Chr: chromosome; Start: beginning of CNV based on build 36.1 of the reference genome; Length: size of CNV in base pairs; Type: duplication (Gain) or deletion (Loss); Controls: prevalence of CNV in control population (4922 individuals); CNVRs that occur in more than one case are listed first; known aneurysm-associated genes are shown in bold type; Genes that are expressed at above average levels in SMCs are underlined; Presence of CNVRs in BCM (B) or familial (F) groups is indicated by parentheses. Footnotes: [a]genes that are potentially disrupted by duplications; [b]$p=0.005$; [c]$p=3x10^{-7}$; [d]genes that overlap with 1-2 additional control CNVs.

Table S3. Rare CNV Regions in FTAAD Patients

Chr	Start	Length	Gene(s)	Copy	Cases	Controls
1	205611610	113158	*CD55*,*CR2*	Loss[b]	1	0
1	234964786	1096137	*RYR2*[a,e],*ACTN2*[a],*MTR*	Gain[c]	1(U)	0
1	239561201	342399	*KMO*,*RGS7*[a],*FH*,*OPN3*,*CHML*,*WDR64*[a]	Gain[d]	1	1
1	244960571	73951	*SCCPDH*[a]	Gain[c]	1	1
2	175176015	519204	*WIPF1*[a],*CHRNA1*,*CHN1*,*ATF2*[a]	Gain[b]	1	0
4	25182217	702217	*SLC34A2*,*KIAA0746*,*C4ORF52*	Loss[b]	1	0
5	10763247	248388	*CTNND2*[a],*DAP*[a]	Gain[b]	1	0
5	121629459	182236	*SNCAIP*[a]	Gain[c]	1	1
7	72360917	1417070	*BAZ1B*,*BCL7B*,*TBL2*,*MLXIPL*,*VPS37D*,*DNAJC30*,*WBSCR22*, *STX1A*,*ABHD11*, *CLDN3*,*CLDN4*,*WBSCR27*,*WBSCR28*,***ELN***,*LIMK1*,*EIF4H*,*LAT2*, *RFC2*,*CLIP2*,*GTF2IRD1*,*GTF2I*	Gain[b]	1	0
10	34837591	356761	*PARD3*[a]	Gain[c]	1	1
10	88690618	308237	*EMILIN3*[a],*SNCG*,*AGAP11*,*C10ORF116*,*GLUD1*[e]	Gain[b]	1(U)	0
10	90468463	113624	*LIPK*,*LIPM*,*LIPN*,*ANKRD22*[a]	Gain[b]	1	0
12	21580167	79075	*GYS2*	Loss[b]	1	0
13	95429222	513627	*UGCGL2*[a],*HS6ST3*[a]	Gain[b]	1	0
15	99293837	172652	*LRRK1*	Loss[b]	1	0
16	15162734	3011916	*MPV17L*,*NDE1*,***MYH11***,*ABCC6*,*ABCC1*,*KIAA0430*	Gain[c]	1(B,U)	5
17	5087194	702887	*RABEP1*,*NUP88*,*RPAIN*,*C1QBP*,*DHX33*,*DERL2*,*MIS12*,*NLRP1*	Gain[b]	1	0
18	73083303	40807	*GALR1*	Gain[b]	1(B)	1
19	17122367	273531	*MYO9B*,*USE1*,*OCEL1*,*NR2F6*,*USHBP1*,*C19orf62*,*ANKLE1*	Loss[b]	1	0
19	46954731	112353	*CEACAM3*,*CEACAM6*[a],*LYPD4*,*DMRTC2*,*RPS19*[a]	Gain[b]	1	0

Chr: chromosome; Start: beginning of CNV based on build 36.1 of the reference genome; Length: size of CNV in base pairs; Type: duplication (Gain) or deletion (Loss); Controls: prevalence of CNV in control population (4922 individuals); known aneurysm-associated genes are shown in bold type; Genes that are expressed at above average levels in vascular SMCs are underlined; Presence of CNVRs in BCM (B) or UTHSCH (U) groups is indicated by parentheses. Footnotes: [a]genes that are potentially disrupted by duplications; [b]p=0.02; [c]p=0.05; [d]p=0.04; [e]genes that overlap with 1-2 additional control CNVs