link between immunological events and IA development.

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Conflict of Interest Disclosures

None

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Figure legend

Figure 1: Segregation of the *TNFRSF13B* deleterious change with the IA phenotype in pedigrees

Figure 2: Schema of the domain structure of full-length *TNFRSF13B*

Figure 3: LD (Linkage Disequilibrium) structure of *TNFRSF13B*

Table 1. Nine Genes First Sequenced in Chromosome 17 Centromere in 58 cases (the first cohort)

Gene Symbol	Gene name	MIM Number	Position	GenBank Accession Number (2006/02/23)	Genomic Region (kb)	mRNA Length (bp)	Number of Exons
TNFRSF13B	tumor necrosis factor receptor superfamily, member 13B	604907	16473152-16439349	NT_010718.15	33.804	879	4
M-RIP	myosin phosphatase-Rho interacting protein	-	16543056-16686620	NT_010718.15	143.565	3,114	29
COPS3	COP9 constitutive photomorphogenic homolog	604665	16782340-16747090	NT_010718.15	35.251	1,269	12
RAI1	retinoic acid induced 1	607642	17181736-17312516	NT_010718.15	130.781	5,718	8
SREBF1	sterol regulatory element binding transcription factor 1	184756	17338043-17312341	NT_010718.15	25.703	3,441	21
GRAP	GRB2-related adaptor protein	604330	18548021-18522034	NT_010718.15	25.988	651	6
MAPK7	mitogen-activated protein kinase 7	602521	18877883-18884469	NT_010718.15	6.587	2,448	7
MFAP4	microfibrillar-associated protein 4	600596	18888110-18883573	NT_010718.15	4.538	765	6
AKAP10	A kinase (PRKA) anchor protein 10	604694	19478745-19405569	NT_010718.15	73.177	1,986	15

Table 2. Characteristics of the first cohort (29 pedigree probands and 29 unrelated cases), the second cohort (304 unrelated cases) and the third cohort (332 unrelated controls)

	Pedigree and Non-pedigree	Non-pedigree cohorts		
	the first cohort	the second cohort	the third cohort	
	29 probands and 29 unrelated cases	304 unrelated cases	332 Controls	#*p* value
Number	58	304	332	
Female, %	70.7	66.8	54.5	0.0016$
Age at diagnosis, y				
Mean±SD	58.6 ± 12.5	59.2 ± 10.6	62.2 ± 9.9	0.00017*
Range	26-78	30-90	40-88	
Hypertension, %	55.2	56.3	42.5	0.0005$
Ever smoker, %	39.7	39.5	37.7	0.13$
Ever drinker, %	43.1	38.5	43.7	0.18$
Family history of IA or SAH, %	58.6	17.4	0	
Ruptured IA, %	62.1	47.0	0	

y: years old

SD: Standard deviation

IA: Intracranial aneurysm

SAH: Subarachnoid hemorrhage

Comparison between 304 unrelated cases (the second cohort) vs. 332 controls (the third cohort)

$ χ^2 test.

* Student's t test.

Table 3. Sequence changes detected in *TNFRSF13B* in the first cohort (29 pedigree probands and 29 unrelated cases), the second cohort (304 unrelated cases) and the third cohort (332 unrelated controls)

Region	position	Contig position	rs number	change	minor allele frequencies in 3 cohorts			GenBank accession number of mRNA and Effect on products	Functional polymorphisms predicted by Polyphen	Allele Frequency	
					first cohort 58 cases	second cohort 304 cases	third cohort 332 controls			world wide	Japanese
								NP_036584			
Promotor	c-247	16472985	rs4985754	G>T	0.362	0.339	0.315			ND	
Exon3		16449689		G>A	0	0.002	0	S70N	beneign		
Exon3		16449677		A>G	0	0.003	0	E74G	possibly damaging		
Exon3		16449672		G>A	0	0.013	0.005	G76S	possibly damaging		
Exon3		16449672		G>T	0.009#	0	0	G76C	probably damaging		
Intron3	IVS3+25	16449376	rs2274892	C>A	0.353	0.358	0.426			NCBI 0.49	ABI 0.36
Intron3	IVS3-1[$]	16441271		G>C	0	0.002	0				
Exon4		16441210		A>T	0.009#	0	0	K154X			
Exon4		16441187		T>C	0	0.003	0.002	C177R	possibly damaging		
Exon4	c.585-586	16441143		insA	0.009#	0	0.002				
Exon5		16440340		C>T	0.345	0.360	0.342	P251L	probably damaging		
Exon5		16440261	rs11078355	C>T	0.138	0.145	0.151	S277S			ABI 0.14
The number of subjects having rare variants					3	14	5				

#: Variants found in only pedigree probands at the first cohort sequences.

$: Change in intronic sequence (splice acceptor site)

IVS: intervening sequence

UTR: untranslated region

ND: no data were available

NCBI: National Center for Biotechnology Information

ABI: Appliedbiosystems; http://www.appliedbiosystems.co.jp/website/jp/information/info.jsp?

Table 4. Four rare non-synonymous changes, a splicing acceptor site change and a frame shift in *TNFRSF13B* and the detected number of subjects in 304 unrelated cases (the second cohort) and 332 controls (the third cohort).
GenBank accession number is NM_012452.

Position	Nucleotide change	Amino acid change	Detected number of subjects unrelated case	control	*p* value
	Rare non-synonymous changes				
Exon3	c. 222G>A	S70N	1	0	
Exon3	c. 234A>G	E74G	2	0	
Exon3	c. 239G>A	G76S	8	3	
Exon4	c. 542T>C	C177R	2	1	
	Splicing acceptor site change				
Intron3	IVS3-1		1	0	
	Frame shift				
Exon4	c.585-586 insertion A		0	1	
	Total		14	5	0.035*

* Fisher's exact test

Table 5. Allele frequencies of *TNFRSF13B* variants in 304 unrelated cases (the second cohort) and 332 controls (the third cohort) and haplotype association study by adjusting for covariates by "THESIAS"

Allele frequency

Hardy-Weinberg equilibrium		
Allele frequency at locus 1[#] (G/T)	0.67 / 0.33	p (HWE) = 0.21
Allele frequency at locus 2[#] (A/C)	0.39 / 0.61	p (HWE) = 0.14
Allele frequency at locus 3[#] (C/T)	0.65 / 0.35	p (HWE) = 0.23
Allele frequency at locus 4[#] (C/T)	0.85 / 0.15	p (HWE) = 0.43

Association study

Haplotype Identifi-Cation Code	Haplotype sequence	Frequency of haplotype unrelated case	control	Odds ratio	(95%CI)	p value
H1	GACC	0.211	0.268	0.69	0.52 - 0.92	0.012*
H2	GACT	0.117	0.131	0.82	0.57 - 1.18	0.29
H3	GCCC	0.251	0.215	1.11	0.79 - 1.42	0.70
H4	TCTC	0.289	0.271	intercept		
Covariate						
Sex (Female vs Male)				2.26	1.55 – 3.30	0.000024
Hypertension				1.97	1.44 – 2.70	0.000027
Smoking (ever smoker vs non smoker)				1.64	1.12 – 2.42	0.011864
Alcohol (ever drinker vs non drinker)				0.91	0.63 – 1.33	0.63

[#] Locus 1: rs4985754, Locus 2: rs2274892, Locus 3: SNP at 16440340, Locus 4: rs11078355

*After Bonferroni correction p_{corr} =0.048

HWE: Hardy-Weinberg equilibrium

CI: Confidence interval