

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Candidate inflammatory and immune response genes

Classification	Gene	Full Name	Chr	Size (bp)	N SNPs Analyzed
Cytokine signaling	<i>IL1A</i>	interleukin-1, alpha proprotein	2	11,479	4
	<i>IL1B</i>	interleukin-1, beta proprotein	2	7,020	9
	<i>IL1RN</i>	interleukin 1 receptor antagonist	2	16,124	15
	<i>IL2</i>	interleukin 2	4	5,025	7
	<i>IL4</i>	interleukin 4	5	200,150	23
	<i>IL5</i>	interleukin 5	5	200,053	34
	<i>IL6</i>	interleukin-6 precursor	7	4,855	7
	<i>IL6R</i>	interleukin-6 receptor isoform 1	1	64,258	15
	<i>IL8</i>	interleukin 8	4	3,211	4
	<i>IL10</i>	interleukin-10 precursor	1	4,892	4
	<i>IL12A</i>	interleukin 12A	3	7,184	7
	<i>IL12B</i>	interleukin 12B	5	15,691	10
	<i>IL12RB1</i>	interleukin 12 receptor, beta 1	19	16,326	4
	<i>IL12RB2</i>	interleukin 12 receptor, beta 2	1	89,537	29
	<i>IL17A</i>	interleukin 17A	6	4,252	12
	<i>IL18</i>	interleukin 18	11	20,867	3
	<i>IL18R1</i>	interleukin 18 receptor 1	2	36,121	12
	<i>IL23A</i>	interleukin 23, alpha subunit p19	12	1,532	1
	<i>IFNG</i>	interferon, gamma	12	4,972	4
	<i>IFNGR1</i>	interferon gamma receptor 1	6	21,947	11
	<i>IFNGR2</i>	interferon gamma receptor 2	21	34,627	6
	<i>MIC1</i>	growth differentiation factor 15	19	3,019	6
	<i>MIF</i>	macrophage migration inhibitory	22	845	12
<i>TGFB1</i>	transforming growth factor, beta 1	19	23,020	6	
<i>TGFBR1</i>	transforming growth factor, beta	9	49,062	8	
<i>TGFBR2</i>	transforming growth factor, beta	3	87,640	47	
<i>TNF</i>	tumor necrosis factor alpha	6	6,236	12	
Eicosanoid signaling	<i>COX-2</i>	prostaglandin-endoperoxide synthase 2	1	8,616	5
Extracellular pattern	<i>MSR1</i>	macrophage scavenger receptor 1	8	84,914	36
	<i>TLR1</i>	toll-like receptor 1	4	8,537	6
	<i>TLR2</i>	toll-like receptor 2	4	21,802	10
	<i>TLR3</i>	toll-like receptor 3	4	15,944	17
	<i>TLR4</i>	toll-like receptor 4	9	13,317	18

recognition	<i>TLR5</i>	toll-like receptor 5	1	33,877	12
	<i>TLR6</i>	toll-like receptor 6	4	33,110	11
	<i>TLR10</i>	toll-like receptor 10	4	10,752	11
NFKB signaling	<i>CHUK</i>	conserved helix-loop-helix	10	41,221	8
	<i>IKBKB</i>	inhibitor of kappa light polypeptide	8	61,352	11
	<i>NFKB1</i>	nuclear factor of kappa light	4	115,974	14
	<i>NFKBIA</i>	nuclear factor of kappa light	14	3,245	17
	<i>RELA</i>	v-rel avian reticuloendotheliosis	11	9,377	3
Selenoproteins	<i>SELS</i>	selenoprotein S	15	6,634	8
	<i>SEP15</i>	15 kDa selenoprotein	1	51,980	7
Immune response	<i>CD14</i>	CD14 molecule	5	1,973	3
	<i>CD3G</i>	T-cell surface glycoprotein CD3	11	9,439	5
	<i>CD68</i>	macrosialin precursor	17	2,625	3
	<i>CD200</i>	OX-2 membrane glycoprotein	3	29,743	11
	<i>CD247</i>	T-cell surface glycoprotein CD3	1	87,971	45
	<i>GUSP11</i>	glucuronidase, beta pseudogene 11	22	78,936	8
	<i>HLA-DRB1</i>	major histocompatibility complex,	6	11,067	7
	<i>IGH</i>	immunoglobulin heavy locus	14	1,255,437	71
	<i>IGJ</i>	immunoglobulin J chain precursor	4	11,091	5
	<i>IGL</i>	immunoglobulin lambda locus	22	884,611	153
	<i>LOC390714</i>	immunoglobulin heavy chain	16	13,406	1
	<i>MS4A1</i>	membrane-spanning 4-domains,	11	14,944	6
	<i>SDC1</i>	syndecan 1 (CD138)	2	24,370	6

Supplementary Table 2. Comparison of minor allele frequency (MAF) of SNPs associated with CCM1 disease severity between CCM1-CHM patients and control subjects from public databases (1000 Genomes - HapMap).

Gene	SNP	Minor Allele	MAF (CCM1-CHM Subjects)	Global MAF (1000 Genomes)	MAF (HapMap MEX)
<i>Cytokine signaling</i>					
<i>IL1RN</i>	rs315947	A	0.26	0.40	0.22
	rs928940	G	0.14	0.32	0.15
<i>IL4</i>	rs9327638	A	0.20	0.09	NA
	rs194395	T	0.22	0.34	0.24
<i>IL5</i>	rs1007270	C	0.20	0.15	0.20
<i>IL6R</i>	rs1146609	A	0.02	0.02	NA
<i>IL12RB1</i>	rs374326	C	0.35	0.19	0.33
<i>IL18R1</i>	rs3732126	C	0.14	0.24	0.24
<i>TGFBR2</i>	rs1249178	T	0.27	0.22	NA
	rs1192442	C	0.36	0.37	0.36
	rs1702578	C	0.42	0.44	0.49
	rs9823731	A	0.36	0.28	NA
<i>Eicosanoid signaling</i>					
<i>COX-2</i>	rs689462	G	0.08	0.08	0.03
<i>Extracellular pattern recognition</i>					
<i>MSR1</i>	rs6248957	C	0.04	0.03	NA
<i>TLR4</i>	rs1075993	T	0.37	0.39	0.43
<i>TLR6</i>	rs7381124	A	0.17	0.08	NA
<i>NFKB signaling</i>					
<i>CHUK</i>	rs4919435	T	0.07	0.06	NA
<i>Selenoproteins</i>					
<i>SELS</i>	rs4965815	T	0.06	0.11	0.23

Immune Response					
CD14	rs778588	C	0.27	0.27	0.19
CD3G	rs1121685	T	0.31	0.38	NA
	rs3181261	T	0.08	0.09	0.03
CD68	rs9901675	A	0.07	0.06	0.04
IGH	rs5776744	T	0.15	0.12	NA
	rs1014775	A	0.11	0.04	NA
	rs5584733	T	0.14	0.17	NA
IGL	rs987710	G	0.29	0.38	0.22
	rs6002270	T	0.03	0.12	NA
	rs1085476	A	0.22	0.32	NA
	rs9622749	G	0.14	0.13	NA
	rs5757039	T	0.10	0.09	NA

Supplementary Table 3. Association of the whole pathway, and sub-pathways of inflammatory and immune response with CCM1 disease severity.

SNP set	N SNPs	P-value		
		ICH	Total Lesions	Large Lesions
Inflammatory/Immune response	1149	0.36	0.005	0.41
• Cytokine signaling	506	0.36	0.12	0.13
• <i>Eicosanoid signaling</i>	6	1	0.006	1
• <i>Extracellular pattern recognition</i>	172	0.39	0.006	0.55
• <i>NFKB signaling</i>	60	0.64	0.70	0.18
• <i>Selenoproteins</i>	20	0.46	0.49	1
• <i>Immune response</i>	385	0.21	0.033	0.74

P-values are corrected for the multiple SNPs within a set (taking account of the LD between these SNPs). *P*-value in bold are considered statistically significant ($P \leq 0.017$).