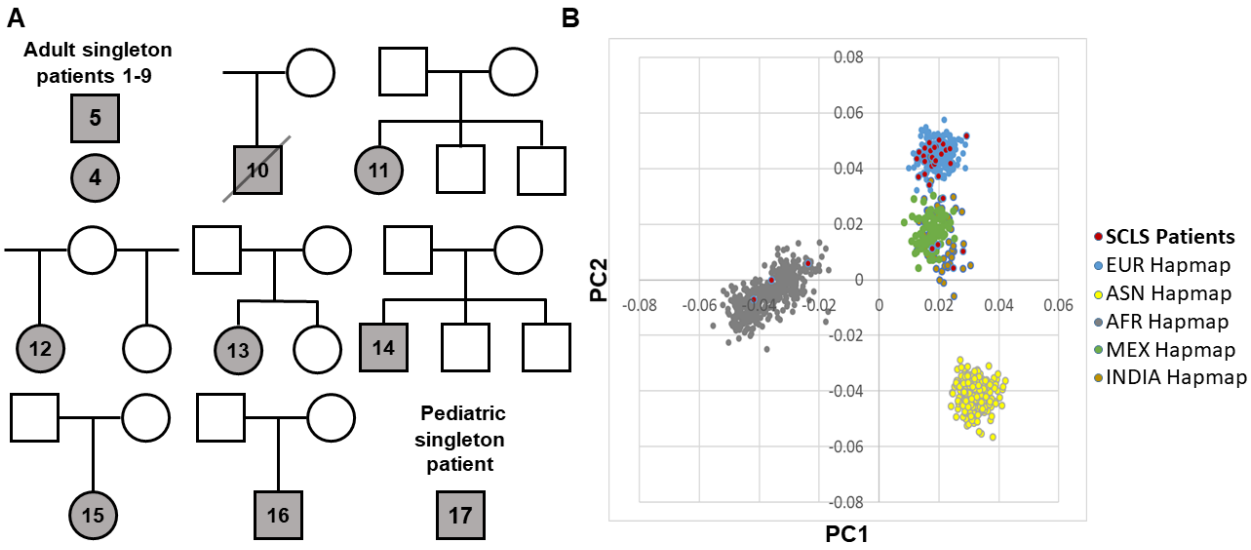


Supplemental Figure 1. (A) Pedigree for systemic capillary leak syndrome patients that underwent whole exome sequencing. Singleton patients 1 through 9 represent the adult cohort while patients 10 through 17 are the pediatric cohort. (B) Principle component analysis of sequenced patients and their relatives by ethnicity.

Supplementary Table 1: Sequencing coverage and quality metrics for all seven-pediatric systemic capillary leak patients and their relatives (26 samples from Yale)

Metric	Mean	Min	Max	Median
Mean independent reads per targeted base	76.5	62.3	91.6	76.2
% of bases mapping to genome	92.55	90.96	93.96	92.47
% of targeted bases with ≥8 independent reads	97.1	87.6	98.3	97.9
Error rate, %	0.28	0.21	0.53	0.25

Supplementary Table 2: Sequencing coverage and quality metrics for the nine-singleton adult systemic capillary leak patients (9 samples from National Institute of Health)

Metric	Mean	Min	Max	Median
Mean independent reads per targeted base	35.8	34.8	36.3	35.9
% of bases mapping to genome	92.80	92.57	92.97	92.80
% of targeted bases with ≥8 independent reads	83.7	83.2	84.0	83.8
Error rate, %	0.20	0.19	0.21	0.20

Supplementary Table 3. Bi-allelic Heterozygous variants identified from 10 single systemic capillary leak patients (Combined annotated dependent depleted (CADD) >15; minor allele frequency less than 0.5%). Genome aggregate database (gnomAD), Sorting Intolerant From Tolerant (SIFT), PolyPhen-2 (PPH2)

Patient ID	**Gene**	**Position (hg19)**	**Nucleotide alteration**	**Alteration in coding region**	**gnomAD**	**gnomAD subpopulation**	**CADD score**	**SIFT**	**PPH2**
2	CACNA1C	12:2788668	c.C5294G	A1765G	7.63e-4	5.42e-4	21.7	T	B
	CACNA1C	12:2800336	c.G6637A	D2213N	1.22e-4	0	29.6	D	D
	PAPLN	14:73716716	c.360delC	C120*	7.13e-4	2.38e-4	.	.	.
	PAPLN	14:73730411	c.C2701G	R901G	7.21e-4	2.29e-4	19.41	T	D
	DNAH17	17:76503418	c.G4618A	V1540M	7.21e-4	1.67e-4	33	.	D
	DNAH17	17:76565555	c.G1099A	E367K	5.86e-4	1.23e-3	22.9	D	B
3	PELP1	17:4577868	c.C1669A	P557T	8.21e-6	1.80e-5	22	T	B
	PELP1	17:4607235	c.C322T	P108S	8.45e-4	1.61e-3	23.8	.	B
6	PXDN	2:1652469	c.A3083G	H1028R	2.89e-4	1.10e-3	24.1	D	D
	PXDN	2:1687867	c.C473T	P158L	3.23e-5	0	21.5	T	B
	AIFM3	22:21328572	c.G497A	R166Q	2.57e-4	3.34e-4	26.7	T	D
	AIFM3	22:21330032	c.C772T	R258*	3.26e-5	6.33e-5	42	.	.
7	TANC2	17:61417560	c.G1452T	Q484H	4.06e-6	8.96e-6	15.72	T	B
	TANC2	17:61497577	c.G4234A	E1412K	4.19e-6	4.58e-5	24.8	D	D
	DOCK6	19:11312585	c.C5668T	R1890C	1.05e-4	9.94e-6	32	D	D
	DOCK6	19:11338140	c.C2828T	A943V	1.52e-5	1.15e-5	20.2	T	B

Supplementary Table 4. Homozygous or X-linked Hemizygous variants identified from all 17 probands (Combined annotated dependent depleted (CADD) >15; minor allele frequency less than 0.5%). Genome aggregate database (gnomAD), Sorting Intolerant From Tolerant (SIFT), PolyPhen-2 (PPH2)

Patient ID	Gene	Position (hg19)	Nucleotide alteration	Alteration in coding region	gnomAD	gnomAD subpopulation	CADD score	SIFT	PPH2
1	SRPX	X:38020242	c.C719G	T240R	5.60e-6	0	27.8	T	D
	PAGE3	X:55287000	c.C286T	P96S	0	0	19.39	T	P
2	F11	4:187201412	c.T901C	F301L	0.0011	0	28.6	D	D
3	SRP68	17:74063305	c.G358A	D120N	0.00095	0.0018	33	D	D
	PIGT	20:44050056	c.G1067A	R356Q	0.0017	0.0019	31	D	D
9	SH3KBP1	X:19626117	c.G944A	R315Q	0	0	24.4	T	B
10	PASD1	X:150839509	c.1072-1G>A	splicing	0	0	.	.	.

Supplementary Table 5: Very Rare Heterozygous loss of function variants identified from 12 systemic capillary leak disease patients without trios (minor allele frequency less than 0.01%) Genome aggregate database (gnomAD)

Patient ID	Gene	Position (hg19)	Nucleotide alteration	Alteration in coding region	gnomAD	gnomAD subpopulation	Gene Intolerance %tile
1	CCDC173	2:170518921	c.G688T	E230X	1.31E-05	2.82E-05	.
	BEST3	12:70048820	c.C1874G	S625X	0	0	55.65%
	STAC2	17:37381696	c.59dupC	P20fs	0	0	20.51%
	TUBB1	20:57594611	c.35delG	C12fs	3.25E-05	5.53E-05	77.36%
2	GSTO2	10:106057334	c.469-2A>G	splicing	7.73E-05	7.17E-05	79.68%
	ZP1	11:60641186	c.C1510T	R504X	0	0	27.79%
	BBS10	12:76740673	c.1091delA	N364fs	6.51E-05	7.91E-06	20.61%
	NANP	20:25604582	c.G3A	M1I	2.58E-05	2.44E-05	22.09%
3	GLB1L3	11:134147643	c.G199T	G67X	2.17E-05	3.95E-05	62.14%
	GNA14	9:80262625	c.A85T	K29X	3.23E-05	6.67E-05	69.37%
4	CEP85L	6:118973861	c.82+1delG	splicing	6.33E-05	6.59E-04	48.05%
	TLR4	9:120475202	c.G676T	E226X	0	0	87.13%
	March8	10:45959422	c.264delG	E88fs	1.55E-04	1.42E-03	50.76%
	DDX49	19:19030585	c.G35A	W12X	4.08E-06	6.64E-06	57.20%
5	TEX261	2:71219114	c.151-1G>C	splicing	2.24E-05	4.95E-05	49.87%
	DOK4	16:57507334	c.935delA	K312fs	0	0	33.25%
6	GMIP	19:19745354	c.2045_2046insG	N682fs	0	0	44.17%
	MANEAL	1:38261459	c.G601T	E201X	0	0	77.46%
	NRDC	1:52257247	c.3163_3164del	N1055fs	0	0	.
	DDX51	12:132627420	c.C523T	Q175X	8.16E-06	6.58E-05	71.22%
	ANKFN1	17:54526496	c.1166delA	E389fs	2.86E-05	6.28E-05	26.71%
	RIT2	18:40323574	c.G538T	E180X	3.62E-05	2.71E-04	32.71%
	AIFM3	22:21330032	c.C772T	R258X	3.26E-05	6.33E-05	82.77%
7	PCDHB13	5:140596087	c.C2392T	Q798X	4.06E-06	0	68.70%
	AGTPBP1	9:88248094	c.G1378T	E460X	0	0	5.55%
	PTPN3	9:112168840	c.1693delC	R565fs	0	0	17.48%
	CKAP2	13:53042428	c.C1492T	R498X	1.78E-05	0	77.25%

	NAGPA	16:5077188	c.1277_1287del	V426fs	3.65E-05	7.16E-05	61.56%
	HAS1	19:52216740	c.C1677G	Y559X	0	0	.
8	ANLN	7:36466557	c.C2803T	R935X	0	0	83.12%
	GDAP1	8:75274205	c.C571T	R191X	0	0	24.48%
	PEX12	17:33903136	c.744dupT	T249fs	8.17E-06	9.06E-06	60.14%
	CEP192	18:13114245	c.7285delC	P2429fs	0	0	82.02%
	ZNF429	19:21720375	c.1521_1525del	K507fs	0	0	84.66%
9	C1orf141	1:67592910	c.13dupA	I5fs	2.47E-05	0	47.60%
	ALDH9A1	1:165648736	c.T873A	C291X	0	0	74.35%
	QTRTD1	3:113785074	c.201-1G>A	splicing	0	0	34.71%
	CPB1	3:148562373	c.A685T	K229X	1.22E-05	1.80-E5	58.94%
	SLC38A6	14:61509864	c.625-1G>C	splicing	4.61E-06	7.04E-06	73.09%
10	NDUFB8	10:102289566	c.C43T	Q15X	0	0	69.73%
12	GCC2	2:109124024	c.G4993T	E1665X	8.22E-06	9.02E-06	5.43%
	BAMBI	10:28970330	c.221delC	A74fs	0	0	38.66%
17	CFAP70	10:75051514	c.2115-1G>A	splicing	0	0	.
	ALDOC	17:26901839	c.A415T	K139X	7.21E-06	1.58E-05	35.41%
	EVPL	17:74015057	c.C1222T	R408X	8.56E-06	9.15E-06	87.21%
	SIRT6	19:4174660	c.1018_1021del	A340fs	5.32E-05	1.35E-04	47.24%

Supplementary Table 6: Gene based collapsing analysis on Very Rare Heterozygous loss of function and missense damaging variants (Combined annotated dependent depleted (CADD) >15; minor allele frequency less than 0.5%). Genome aggregate database (gnomAD), Sorting Intolerant From Tolerant (SIFT), PolyPhen-2 (PPH2)

Pt	Gene	Position (hg19)	Nucleotide alteration	Alteration in coding region	gnomAD	gnomAD subpopulation	CADD	SIFT	PPH2	Gene Intolerance %tile	P val
5	NDRG2	14:21485816	c.G1055T	S352I	0	0	28.7	D	P	53.42%	2.98E-03
6	NDRG2	14:21486942	c.G793A	A265T	0	0	33	D	D	53.42%	2.98E-03
1	ZDHHC23	3:113667807	c.A158T	D53V	4.06E-06	8.95E-06	26.6	D	P	22.02%	3.54E-03
9	ZDHHC23	3:113675215	c.A902G	H301R	4.06E-06	8.95E-06	27.2	D	D	22.02%	3.54E-03
3	GLB1L3	11:134147643	c.G199T	G67X	2.17E-05	3.96E-05	36	.	.	62.14%	8.81E-03
7	GLB1L3	11:134151291	c.A383G	H128R	4.06E-06	8.95E-06	24.1	D	D	62.14%	8.81E-03
12	TMCO3	13:114150180	c.C284G	T95R	4.06E-06	8.95E-06	24.9	D	D	85.00%	9.36E-03
5	TMCO3	13:114193812	c.C1680A	F560L	3.23E-05	6.66E-05	22.3	D	D	85.00%	9.36E-03
4	JUP	17:39919362	c.G1370A	C457Y	0	0	25.7	D	D	31.26%	1.12E-02
7	JUP	17:39925357	c.C571T	R191C	1.10E-05	1.59E-05	26.2	D	P	31.26%	1.12E-02
7	KIF11	10:94353137	c.C5A	A2E	0	0	32	D	D	68.02%	2.16E-02
12	KIF11	10:94413459	c.G3077T	G1026V	7.22E-06	7.90E-06	22.8	D	B	68.02%	2.16E-02
10	TMEM132D	12:129558977	c.G2743A	D915N	1.08E-05	2.37E-05	27.4	D	D	4.19%	2.31E-02
4	TMEM132D	12:130185014	c.G309T	E103D	3.23E-05	0	21	T	D	4.19%	2.31E-02
8	ATP10A	15:25953367	c.C2425T	R809C	4.04E-06	8.95E-06	35	D	D	61.68%	4.08E-02
4	ATP10A	15:25959015	c.G2150A	R717Q	4.06E-06	2.98E-05	28.5	D	D	61.68%	4.08E-02
3	BRWD1	21:40570882	c.T5460G	S1820R	4.07E-06	9.00E-06	23.4	D	D	2.33%	8.76E-02
1	BRWD1	21:40636577	c.G1694T	R565L	0	0	34	D	D	2.33%	8.76E-02
12	ANK2	4:114260448	c.G3863A	C1288Y	4.06E-06	8.95E-06	28.1	D	D	1.06%	2.04E-01
9	ANK2	4:114278865	c.A9091G	S3031G	0	0	22.6	D	B	1.06%	2.04E-01