Systematic approach revealed *SERPING1* splicing-affecting variants to be highly represented in the Czech national HAE cohort

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Supplementary material

- Tables S1-S3
- Supplementary methods
- Figures S1, S2

Sample ID	Year of birth	Causal variant	Protein change	Method	c.-21T>C	Symptomatic/Asymptomatic	Age of onset	Age of diagnosis	No. of edemas per year	Long term prophylaxis	Clinical severity score	C1-INH [g/l]	C1-INH Normal values [g/l]	C1-INH evaluation	C1-INH function [%]	C1-INH func. Normal values [%]	C1-INH function evaluation	C4 [g/l]	C4 Normal values [g/l]	C4 evaluation
P00101#	1943	c.855_856del	p.(Arg286Profs*18)	DGGE + NGS	not	S	2	49	24			0.063	0.2-0.35	L				0.04	0.15-0.4	L
P00102#	1965	c.855_856del	p.(Arg286Profs*18)	DGGE + Sanger	NA	S	21	27	12			0.064	0.2-0.35	L				0.07	0.2-0.5	L
P00201#	1975	c.1249+5G>A		DGGE + Sanger	not	S	13	22	24			0.069	0.2-0.35	L				0.07	0.1-0.4	L
P00301#	1946	c.685+2_685+13del		DGGE + Sanger	not	S	13	31	30	yes	8	0.054	0.15-0.35	L				0.05	0.1-0.4	L
P00302	1975	c.685+2_685+13del		DGGE + Sanger	TRANS	S	3	3	25	yes	10	0.068	0.25-0.34	L				0.06	0.1-0.4	L
P00303	1975	c.685+2_685+13del		DGGE + Sanger	not	S	30	3	1	yes	5	0.04	0.15-0.35	L				0.06	0.1-0.4	L
P00304	2006	c.685+2_685+13del		Sanger	not	NA				no	2									
P00401#	1947	c.1361T>G, c.564_569dup†	p.Val454Gly, p.Asn188_Thr189dup†	DGGE + Sanger	NA	S	21	40	14	yes	5	0.137	0.25-0.34	L				0.06	0.1-0.34	L
P00501#	1947	c.1322T>A	p.Met441Lys	DGGE + Sanger	not	S	6	42	15	yes	9	0.05	0.15-0.35	L	44	>68	L	0.06	0.14-0.35	L
P00502	1969	c.1322T>A	p.Met441Lys	DGGE + Sanger	not	S	19	19	12	yes	7	0.07	0.15-0.35	L	57	>68	L	0.06	0.14-0.35	L
P00503	2001	c.1322T>A	p.Met441Lys	DGGE + NGS	not	S		6	2	no	3	0.04	0.15-0.35	L	61	>68	L	0.1	0.14-0.35	L
P00601	1958	c.305_317del	p.(Pro102Leufs*42)	DGGE + Sanger	not	S	16	20	7	yes	6	0.07	0.15-0.35	L	22	>68	L	0.05	0.1-0.4	L
P00602	1957	c.305_317del	p.(Pro102Leufs*42)	DGGE + Sanger	TRANS	S	18	22	25	yes	8	0.03	0.15-0.35	L	15	>68	L	0.02	0.1-0.4	L
P00603	1977	c.305_317del	p.(Pro102Leufs*42)	DGGE + Sanger	not	S	6	15	13	yes	8	0.037	0.25-0.34	L	21	>68	L	0.03	0.14-0.35	L
P00604	2011	c.305_317del	p.(Pro102Leufs*42)	Sanger	not	A		2		no		0.05	0.15-0.36	L				0.04	0.14-0.35	L
P00605	1934	c.305_317del	p.(Pro102Leufs*42)	DGGE + Sanger	not	S	19					0.13	0.15-0.35	L				0.07	0.1-0.4	L
P00606	1972	c.305_317del	p.(Pro102Leufs*42)	Sanger	NA	S	28	28	12	yes	7	0.03	0.15-0.35	L	0	>68	L	0.02	0.1-0.4	L
P00607	1998	c.305_317del	p.(Pro102Leufs*42)	Sanger	not	S	16	16	10	yes	8	0.04	0.15-0.35	L	22	>68	L	0.03	0.1-0.4	L
P00701#	1973	c.1202T>A	p.Ile401Asn	DGGE + Sanger	not	S	10	10	8	yes	7	0.04	0.15-0.35	L	18	>68	L	0.04	0.14-0.34	L
P00702	1951	c.1202T>A	p.Ile401Asn	DGGE + Sanger	not	S	10	35	3	yes		0.05	0.15-0.35	L	57	>68	L	0.1	0.14-0.35	L
P00801#	1974	c.793T>G	p.Trp265Gly	DGGE + Sanger	not	S	19	23	6	yes	8	0.018	0.15-0.35	L	52	>68	L	0.02	0.15-0.40	L
P00802	1948	c.793T>G	p.Trp265Gly	DGGE + Sanger	not	S	25	58	2	no	3	0.043	0.15-0.35	L	61	>68	L	0.02	0.15-0.40	L
P00803	1958	c.793T>G	p.Trp265Gly	DGGE + Sanger	not	S	16	48	5	no	7	0.038	0.15-0.35	L	0	>68	L	0.02	0.15-0.40	L

Sample ID	Year of birth	Causal variant	Protein change	Method	c.-21T>C	Symptomatic/Asymptomatic	Age of onset	Age of diagnosis	No. of edemas per year	Long term prophylaxis	Clinical severity score	C1-INH [g/l]	C1-INH Normal values [g/l]	C1-INH evaluation	C1-INH function [%]	C1-INH func. Normal values [%]	C1-INH function evaluation	C4 [g/l]	C4 Normal values [g/l]	C4 evaluation
P00901#	1966	c.1115del	p.(Gln372Argfs*25)	DGGE + Sanger	TRANS	S	4	4	27	yes	10	0.08	0.15-0.35	L	31	>68	L	0.02	0.14-0.35	L
P00902	1994	c.1115del	p.(Gln372Argfs*25)	DGGE + Sanger	not	S	8		23	yes	7	0.05	0.15-0.35	L	29	>68	L	0.02	0.14-0.35	L
P01001	1985	c.1396C>T	p.Arg466Cys	DGGE + Sanger	not	S	5	5	24	yes	10	0.47	0.15-0.35	H	49	>68	L	0.1	0.14-0.35	L
P01002	2008	c.1396C>T	p.Arg466Cys	Sanger	not	S	4	4	6	no	6	0.43	0.15-0.35	H	55	>68	L	0.08	0.14-0.35	L
P01003	2011	c.1396C>T	p.Arg466Cys	DGGE + Sanger	not	S	6	1	6	no	5	0.42	0.15-0.35	H	45	>68	L	0.1	0.14-0.35	L
P01101#	1986	c.1225_1249+19del		Sanger	not	S	15	17	39	yes	8	0.04	0.21-0.39	L	24	>68	L	0.019	0.1-0.4	L
P01102	2004	c.1225_1249+19del		Sanger	not	S	6	1	2	no	4	0.076	0.21-0.39	L	37	>68	L	0.05	0.1-0.38	L
P01201#	1957	c.1046T>C	p.Leu349Pro	DGGE + Sanger	not	S	27	47	14	yes	4	0.05	0.15-0.35	L				0.05	0.14-0.34	L
P01202	2002	c.1046T>C	p.Leu349Pro	DGGE + Sanger	not	S	9	10	6	no	5	0.05	0.15-0.35	L	40	>68	L	0.05	0.1-0.4	L
P01301#	2004	c.550G>A	p.Gly184Arg	Sanger	not	S	7	9	20	yes	8	0.07	0.15-0.36	L	29	>68	L	0.03	0.14-0.35	L
P01401	1984	c.1284_1285del	p.(Cys428Trpfs*44)	Sanger	not	S	17	21	27	yes	8	0.095	0.15-0.35	L	48	>68	L	0.11	0.15-0.40	L
P01501	1975	c.743C>G	p.Pro248Arg	Sanger	not	S	25	35	5	yes	6	0.1	0.15-0.36	L	39	>68	L	0.05	0.14-0.35	L
P01502	2006	c.743C>G	p.Pro248Arg	Sanger	not	S	6	10	3	no		0.09	0.15-0.36	L	57	>68	L	0.03	0.14-0.35	L
P01503	2009	c.743C>G	p.Pro248Arg	Sanger	not	S	8	7	4	no	4	0.08	0.15-0.36	L	44	>68	L	0.05	0.14-0.35	L
P01601	1958	EX7del		MLPA	not	NA														
P01602	1981	EX7del		MLPA	not	S			9	no	2	0.031	0.21-0.33	L	15	>68	L	0.02	0.1-0.38	L
P01603	2013	EX7del		MLPA	not	A		6				0.03	0.21-0.34	L	21	>68	L	0.02	0.1-0.38	L
P01604	1986	EX7del		MLPA	not	NA				no	5									
P01701	1981	variant not detected			ND	S	23	35	2	no		0.059	0.21-0.39	L	36	>68	L	0.08	0.1-0.38	L
P01901	1992	c.506T>C	p.Phe169Ser	Sanger	not	S	18	18	1	no		0.07	0.15-0.36	L	30	>68	L	0.04	0.14-0.35	L
P01902	2021	c.506T>C	p.Phe169Ser	Sanger	not	NA														
P02001	1985	c.1397G>A	p.Arg466His	Sanger	not	S		32	6	no		0.36	0.15-0.36	N	46	>68	L	0.13	0.14-0.35	L
P02101	1994	EX1-8del		MLPA	not	S	14	23	9	no	6	0.047	0.21-0.39	L	20	>68	L	0.05	0.1-0.38	L
P02201	1994	c.550+3A>C		Sanger	not	S	16	23	24	yes	6	0.05	0.15-0.35	L	38	>68	L	0.08	0.1-0.4	L
P02301	1965	c.51+5G>A		Sanger	not	S	14	24	5	no	2	0.086	0.21-0.33	L	27	>68	L	0.1	0.1-0.38	N
P02401	1973	EX4del		MLPA	not	NA														
P02501	1961	c.1396C>T	p.Arg466Cys	Sanger	not	S	20	58	15	yes	4	0.284	0.15-0.35	N	37	>68	L			
P02502	1987	c.1396C>T	p.Arg466Cys	Sanger	not	S	33	34	1	no		0.45	0.15-0.35	H	67	>68	L	0.14	0.15-0.40	L
P02503	1991	c.1396C>T	p.Arg466Cys	Sanger	not	S	15	29	3	no	3	0.439	0.15-0.35	H	51	>68	L			
P02601	1962	c.706T>G	p.Phe236Val	DGGE + Sanger	not	NA														
P02602#	1994	c.706T>G	p.Phe236Val	Sanger	NA	S	6	12	25	yes	9	0.06	0.15-0.36	L	63	>68	L	0.05	0.14-0.35	L
P02701	1979	c.1397G>A	p.Arg466His	Sanger	not	S	25	40	5	no	2	0.357	0.21-0.39	N	37	>68	L	0.06	0.1-0.38	L
P02702	2011	c.1397G>A	p.Arg466His	Sanger	not	A		8				0.35	0.21-0.39	N	75	>68	N	0.06	0.1-0.38	L
P02801	2011	c.686-1G>T		Sanger	ND	S	4	8	17	no	9	0.047	0.21-0.39	L	31	>68	L	0.05	0.1-0.38	L
P02901	1977	c.1029+384A>G		Sanger	TRANS	S	21	42	2	no	1	0.064	0.15-0.35	L	32	>68	L	0.08	0.14.0.35	L
P02902	1949	c.1029+384A>G		NGS	not	S	72	72	3			0.07	0.21-0.39	L	41	>68	L	0.11	0.1-0.38	N
P03001	1976	c.686-7C>G		Sanger	not	S	15	43	1	no	3	0.058	0.21-0.39	L	31	>68	L	0.05	0.1-0.38	L
P03002	2002	c.686-7C>G		Sanger	not	S	10	18	4	no	5	0.05	0.21-0.39	L	25	>68	L	0.03	0.1-0.38	L
P03101	1984	c.722G>C	p.Arg241Pro	Sanger	not	S	34	35	2	no	3	0.115	0.15-0.35	L	43	>68	L	0.07	0.15-0.40	L
P03102	1945	c.722G>C	p.Arg241Pro	Sanger	not	S	32	75	1	no	1	0.121	0.15-0.35	L	58	>68	L	0.1	0.15-0.41	L
P03301	1971	EX4del		MLPA	not	S	16	49	16	no	5	0.044	0.21-0.39	L	32	>68	L	0.05	0.1-0.38	L
P03401#	1970	c.600dup	p.(Lys201Glnfs*56)	DGGE + Sanger	not	S	14		24	yes	5									
P03402	1942	c.600dup	p.(Lys201Glnfs*56)	Sanger	not	NA				yes	4									
P03501	1987	c.151_152del	p.(Ser51Glnfs*6)	Sanger	not	S	5	33	3	no	5	0.05	0.15-0.36	L	31	>68	L	0.02	0.14-0.35	L
P03502	2019	c.151_152del	p.(Ser51Glnfs*6)	Sanger	not	S	2	1	2			0.11	0.15-0.36	L	40	>68	L	0.04	0.14-0.35	L
P03701#	1990	c.685+1del		DGGE + Sanger	not	S	7	14	20	yes	6	0.037	0.15-0.35	L	37	>68	L	0.03	0.14-0.35	L
P03702	2001	c.685+1del		Sanger	not	NA				no										
P03703	1967	c.685+1del		Sanger	not	NA				no										
P03704	1999	c.685+1del		Sanger	not	NA				no	3									
P03801#	1973	c.551-2A>G		DGGE + Sanger	not	S	10	18	24	yes	5	0.054	0.21-0.39	L	5	>68	L	0.035	0.1-0.38	L
P03802	1979	c.551-2A>G		Sanger	not	S	17	28	3	no	7	0.039	0.21-0.39	L	38	>68	L	0.023	0.1-0.38	L
P03803	2013	c.551-2A>G		Sanger	not	S	6	2	3	no		0.04	0.21-0.39	L	20	>68	L	0.02	0.1-0.38	L
P03804	2000	c.551-2A>G		Sanger	not	S	9	11	9	yes	8	0.053	0.21-0.39	L	39	>68	L	0.054	0.1-0.38	L

Sample ID	Year of birth	Causal variant	Protein change	Method	c.-21T>C	Symptomatic/Asymptomatic	Age of onset	Age of diagnosis	No. of edemas per year	Long term prophylaxis	Clinical severity score	C1-INH [g/l]	C1-INH Normal values [g/l]	C1-INH evaluation	C1-INH function [%]	C1-INH func. Normal values [%]	C1-INH function evaluation	C4 [g/l]	C4 Normal values [g/l]	C4 evaluation
P03805	1998	c.551-2A>G		Sanger	not	S	11	13	15	yes	5	0.034	0.21-0.39	L	27	>68	L	0.03	0.1-0.38	L
P03806	1948	c.551-2A>G		Sanger	not	S	30	59	6			0.066	0.21-0.39	L	57	>68	L	0.101	0.1-0.38	N
P03807	2007	c.551-2A>G		Sanger	not	S	7	0	2	yes	4	0.077	0.21-0.39	L	44	>68	L	0.07	0.1-0.38	L
P03808	2016	c.551-2A>G		Sanger	not	S		2	2			0.039	0.21-0.39	L	23	>68	L	0.03	0.1-0.38	L
P03901	2009	EX4del		MLPA	not	S	6	12				0.08	0.15-0.36	L	35	>68	L	0.04	0.14-0.35	L
P04001	1993	EX4del		MLPA	not	S	12	13	3	no	4	0.04	0.15-0.36	L	11	>68	L	0.03	0.14-0.35	L
P04002	1964	EX4del		MLPA	not	S	40	46	4	no	4	0.06	0.15-0.36	L	47	>68	L	0.03	0.14-0.35	L
P04101	1983	EX4del		MLPA	not	NA														
P04201#	1984	c.305_317del	p.(Pro102Leufs*42)	DGGE + Sanger	not	S	10	10	10	yes	8	0.05	0.15-0.36	L	33	>68	L	0.03	0.14-0.35	L
P04202	1991	c.305_317del	p.(Pro102Leufs*42)	Sanger	not	S	10	10	13	yes	6	0.04	0.15-0.36	L	32	>68	L	0.02	0.14-0.35	L
P04203	1969	c.305_317del	p.(Pro102Leufs*42)	Sanger	not	NA				no	3									
P04204	2004	c.305_317del	p.(Pro102Leufs*42)	Sanger	not	S	9	12	2	no		0.07	0.15-0.36	L	30	>68	L	0.05	0.14-0.35	L
P04205	1963	c.305_317del	p.(Pro102Leufs*42)	Sanger	not	S	17	39	2	no	3	0.03	0.15-0.35	L	31	>68	L	0.03	0.14-0.34	L
P04206	1990	c.305_317del	p.(Pro102Leufs*42)	Sanger	not	S	13	13	28	no	4	0.04	0.15-0.35	L	22	>68	L	0.02	0.14-0.34	L
P04207	2016	c.305_317del	p.(Pro102Leufs*42)	Sanger	not	A				no		0.12	0.15-0.35	L	56	>68	L	0.08	0.14-0.34	L
P04301#	1978	c.686-12A>G		DGGE + Sanger	not	S	10	30	7	yes	5	0.057	0.21-0.39	L	44	>68	L	0.066	0.1-0.38	L
P04401	1997	EX4del		MLPA	not	NA														
P04402	1967	EX4del		MLPA	not	NA														
P04501	1977	c.-22-19_-22-4del		DGGE + Sanger	not	S	23		12	yes	4	0.06	0.15-0.36	L	44	>68	L	0.03	0.14-0.35	L
P04502	2000	c.-22-19_-22-4del		Sanger	not	A		13		no		0.06	0.15-0.36	L	62	>68	L	0.05	0.14-0.35	L
P04601#	1994	c.1283del	p.(Cys428Leufs*3)	DGGE + Sanger	not	S	4	15	11	yes	8	0.089	0.15-0.35	L	43	>68	L	0.068	0.1-0.38	L
P04701	1967	EX7del		MLPA	not	S	15	41	6	yes	6	0.048	0.15-0.35	L	49	>68	L	0.06	0.15-0.40	L
P04702	2002	EX7del		MLPA	not	S	17	6	2	no	4	0.095	0.15-0.35	L	38	>68	L	0.06	0.15-0.40	L
P04801#	1979	c.897G>A	p.(Trp299*)	DGGE + Sanger	TRANS	S	3	10	17	yes	8	0.03	0.15-0.35	L	37	>68	L	0.02	0.1-0.4	L
P04802	1957	c.897G>A	p.(Trp299*)	Sanger	not	S		30	5	yes	2	0.05	0.15-0.36	L	36	>68	L	0.09	0.14-0.35	L
P04803	2010	c.897G>A	p.(Trp299*)	Sanger	not	S	4	1	14	no	6	0.09	0.15-0.35	L	36	>68	L	0.07	0.14-0.34	L
P04901	1968	c.551-2A>G		DGGE + Sanger	not	S	10	28	15	yes	9	0.06	0.21-0.39	L	60	>68	L	0.03	0.1-0.38	L
P04902	1991	c.551-2A>G		DGGE + Sanger	not	S	17	17	17	yes	8	0.066	0.21-0.39	L	40	>68	L	0.089	0.1-0.38	L
P04903	2006	c.551-2A>G		Sanger	not	S	8	8	4	no	3	0.038	0.21-0.39	L	32	>68	L	0.03	0.1-0.38	L
P05001	1993	c.1397G>A	p.Arg466His	DGGE + Sanger	TRANS	S	13	16	60	yes	8	0.333	0.15-0.35	N	56	>68	L	0.055	0.15-0.40	L
P05002	2016	c.1397G>A	p.Arg466His	Sanger	TRANS	S	2	2	4	no	6	0.383	0.15-0.35	H	27	>68	L	0.03	0.15-0.40	L
P05003	1970	c.1397G>A	p.Arg466His	DGGE + Sanger	not	S	23	39	7	yes	7	0.369	0.15-0.35	H	27	>68	L	0.07	0.15-0.40	L
P05004	1988	c.1397G>A	p.Arg466His	Sanger	not	S	30	26	1	no	1	0.373	0.15-0.35	H	42	>68	L	0.05	0.15-0.40	L
P05101	1965	c.1361T>G	p.Val454Gly	DGGE + Sanger	not	S	22	44	4	yes	4	0.158	0.21-0.39	L	44	>68	L	0.053	0.1-0.38	L
P05102	1994	c.1361T>G	p.Val454Gly	Sanger	not	A		19		no		0.164	0.21-0.39	L	25	>68	L	0.06	0.1-0.38	L
P05103	1961	c.1361T>G	p.Val454Gly	DGGE + Sanger	not	S	17	36	3	no	7	0.176	0.21-0.39	L	18	>68	L	0.088	0.1-0.38	L
P05104	1993	c.1361T>G	p.Val454Gly	Sanger	not	S	18	18	1	yes	3	0.2	0.21-0.39	L	54	>68	L	0.092	0.1-0.38	L
P05201	1973	c.1460_1466del	p.(Lys487Metfs*87)	DGGE + Sanger	not	S	19	36	32	yes	8	0.03	0.15-0.35	L	0	>68	L	0.02	0.14-0.34	L
P05202	1949	c.1460_1466del	p.(Lys487Metfs*87)	Sanger	not	S	14	60	24	yes	8	0.03	0.15-0.35	L	0	>68	L	0.02	0.1-0.4	L
P05203	2010	c.1460_1466del	p.(Lys487Metfs*87)	Sanger	not	S	4	2	20	no	9	0.06	0.15-0.35	L	15	>68	L	0.06	0.14-0.34	L
P05204	1972	c.1460_1466del	p.(Lys487Metfs*87)	Sanger	not	S	13	37	20	yes	6	0.05	0.15-0.35	L	0	>68	L	0.04	0.1-0.4	L
P05205	2010	c.1460_1466del	p.(Lys487Metfs*87)	Sanger	not	S	2	1	4	no	9	0.04	0.15-0.35	L	46	>68	L	0.06	0.1-0.4	L
P05301	1976	c.795_796delGGinsT, c.785T>C†	p.(Trp265Cysfs*14), p.Ile262Thr†	DGGE + Sanger	not	S	15	33	25	yes	6	0.084	0.21-0.39	L	61	>68	L	0.038	0.1-0.38	L
P05302	2002	c.795_796delGGinsT, c.785T>C†	p.(Trp265Cysfs*14), p.Ile262Thr†	DGGE + Sanger	not	S	9	8	1	no	4	0.041	0.21-0.39	L	20	>68	L	0.05	0.1-0.38	L
P05401	1992	c.1249+1G>A		DGGE + Sanger	not	S	13	17	12	yes	4	0.13	0.15-0.36	L	53	>68	L	0.07	0.14-0.35	L
P05501	2001	c.726_777del	p.(Leu243Serfs*19)	DGGE + Sanger	not	S	9	10	6	no	5	0.038	0.15-0.35	L	32	>68	L	0.02	0.15-0.40	L

Sample ID	Year of birth	Causal variant	Protein change	Method	c.-21T>C	Symptomatic/Asymptomatic	Age of onset	Age of diagnosis	No. of edemas per year	Long term prophylaxis	Clinical severity score	C1-INH [g/l]	C1-INH Normal values [g/l]	C1-INH evaluation	C1-INH function [%]	C1-INH func. Normal values [%]	C1-INH function evaluation	C4 [g/l]	C4 Normal values [g/l]	C4 evaluation
P05502	1992	c.726_777del	p.(Leu243Serfs*19)	Sanger	not	S	20	25	4	yes	5	0.083	0.15-0.35	L	59	>68	L	0.06	0.15-0.40	L
P05503	1970	c.726_777del	p.(Leu243Serfs*19)	Sanger	not	S	7	41	1	yes	6	0.083	0.15-0.35	L	54	>68	L	0.08	0.15-0.40	L
P05504	1975	c.726_777del	p.(Leu243Serfs*19)	Sanger	not	S	15	36	4	no	4	0.128	0.15-0.35	L				0.12	0.15-0.40	L
P05505	1941	c.726_777del	p.(Leu243Serfs*19)	Sanger	not	S	68	73	1	no	2	0.181	0.15-0.35	N	71	>68	N	0.23	0.15-0.40	N
P05506	1996	c.726_777del	p.(Leu243Serfs*19)	Sanger	not	S	22		1	no		0.063	0.21-0.39	L	48	>68	L	0.06	0.1-0.38	L
P05507	2000	c.726_777del	p.(Leu243Serfs*19)	Sanger	not	S	8	9	22	yes	7	0.054	0.15-0.35	L	26	>68	L	0.04	0.15-0.40	L
P05601	1975	c.1361T>G	p.Val454Gly	DGGE + Sanger	not	S	19	36	33	yes	8	0.153	0.21-0.39	L	41	>68	L	0.09	0.1-0.38	L
P05602	2002	c.1361T>G	p.Val454Gly	Sanger	not	A		10		no		0.168	0.21-0.39	L	54	>68	L	0.092	0.1-0.38	L
P05701	1984	c.503C>A	p.Ala168Asp	DGGE + Sanger	CIS	S	26	27	55	no	6	0.042	0.21-0.39	L	24	>68	L	0.034	0.1-0.38	L
P05702	2016	c.503C>A	p.Ala168Asp	Sanger	CIS	A		3				0.085	0.21-0.39	L	57	>68	L	0.04	0.1-0.38	L
P05703	2019	c.503C>A	p.Ala168Asp	Sanger	CIS	A		2				0.144	0.21-0.39	L	70	>68	N	0.11	0.1-0.38	N
P05801	1976	c.1249+2T>C		DGGE + Sanger	not	S	18	36	2	yes	3	0.04	0.15-0.36	L	40	>68	L	0.06	0.14-0.35	L
P05901	1976	c.1346T>C	p.Leu449Pro	DGGE + Sanger	NA	S	6		21	yes	9	0.05	0.15-0.36	L	35	>68	L	0.05	0.14-0.35	L
P06001	1965	EX4del		MLPA	not	S	6	25	26	yes	9	0.1	0.15-0.36	L	54	>68	L	0.05	0.14-0.35	L
P06002	2006	EX4del		MLPA	not	S	1	6	19	yes	7	0.12	0.15-0.36	L	44	>68	L	0.11	0.14-0.35	L
P06003	1988	EX4del		MLPA	not	S	7	5	40	yes	9	0.07	0.15-0.36	L	60	>68	L	0.07	0.14-0.35	L
P06004	2018	EX4del		MLPA	not	A		2				0.11	0.15-0.36	L	75	>68	N	0.09	0.14-0.35	L
P06101	1975	c.1396C>T	p.Arg466Cys	DGGE + Sanger	not	S	10	37	8	yes	9	0.765	0.21-0.39	H	29	>68	L	0.042	0.1-0.38	L
P06102	1952	c.1396C>T	p.Arg466Cys	DGGE + Sanger	not	S	23	60	13	no	2	0.286	0.21-0.39	N	26	>68	L	0.06	0.1-0.38	L
P06201	1976	EX4del		MLPA	not	S	25	25	17	yes	6	0.11	0.15-0.36	L	48	>68	L	0.03	0.14-0.35	L
P06301	1977	c.498C>A	p.Asn166Lys	DGGE + Sanger	TRANS	S	12		23	yes	8	0.05	0.15-0.36	L	12	>68	L	0.05	0.14-0.35	L
P06401	1984	c.1284_1285del	p.(Cys428Trpfs*44)	DGGE + Sanger	not	S			1	yes	7	0.08	0.15-0.36	L	55	>68	L	0.05	0.14-0.35	L
P06501	1992	c.1420C>T	p.(Gln474*)	DGGE + Sanger	not	S	3	19	37	yes	10	0.04	0.15-0.36	L	28	>68	L	0.07	0.14-0.35	L
P06502	1965	c.1420C>T	p.(Gln474*)	Sanger	not	S	3	46	6	yes	9	0.04	0.15-0.36	L	40	>68	L	0.07	0.14-0.35	L
P06503	2018	c.1420C>T	p.(Gln474*)	Sanger	not	S	3	19	37	no		0.04	0.15-0.36	L	28	>68	L	0.03	0.14-0.35	L
P06601	1966	c.1195C>T	p.Pro399Ser	DGGE + Sanger	TRANS	S	13	46	30	yes	4	0.04	0.21-0.39	L	11	>68	L	0.034	0.1-0.38	L
P06602	1988	c.1195C>T	p.Pro399Ser	Sanger	not	A		25				0.043	0.21-0.39	L	20	>68	L	0.1	0.1-0.38	N
P06701	1972	c.1361T>G	p.Val454Gly	DGGE + Sanger	not	S		37	6	yes	4	0.21	0.15-0.36	N	53	>68	L	0.09	0.14-0.35	L
P06801	1991	c.1029+384A>G		Sanger	not	S	10	10	27	no	8	0.058	0.21-0.39	L	0	>68	L	0.02	0.1-0.38	L
P06901	1978	c.1397G>A	p.Arg466His	Sanger	not	S	31	34	36			0.3	0.15-0.36	N	79	>68	N	0.06	0.14-0.35	L
P06902	2019	c.1397G>A	p.Arg466His	Sanger	NA	NA														
P06903	2017	c.1397G>A	p.Arg466His	Sanger	NA	NA														
P07001	1993	c.614G>A	p.Cys205Tyr	Sanger	not	S	10	17	14	no	6	0.069	0.21-0.39	L	31	>68	L	0.05	0.1-0.38	L
P07002	1971	c.614G>A	p.Cys205Tyr	Sanger	not	S	43	43	1			0.075	0.21-0.39	L	50	>68	L	0.018	0.1-0.38	L
P07003	1964	c.614G>A	p.Cys205Tyr	Sanger	not	S	29	49	4	yes	5	0.069	0.21-0.39	L	33	>68	L	0.07	0.1-0.38	L
P07101	1992	c.1036C>T	p.(Gln346*)	Sanger	not	S	11	18	22	yes	8	0.032	0.21-0.39	L	27	>68	L	0.04	0.1-0.38	L
P07102	1968	c.1036C>T	p.(Gln346*)	Sanger	not	S	23	42	24	yes	7	0.037	0.21-0.39	L	37	>68	L	0.03	0.1-0.38	L
P07103	1994	c.1036C>T	p.(Gln346*)	Sanger	not	S	16	11	21	no	5	0.044	0.21-0.39	L	35	>68	L	0.059	0.1-0.38	L
P07201	1970	EX4del		MLPA	TRANS	S	15	30	7	no	6	0.07	0.21-0.39	L	45	>68	L	0.05	0.1-0.38	L
P07202	1991	EX4del		MLPA	not	S	13	19	8	yes	8	0.068	0.21-0.39	L	37	>68	L	0.056	0.1-0.38	L
P07301#	1969	c.550G>T	p.Gly184Trp	DGGE + Sanger	not	S	22	29	1	yes	4	0.085	0.21-0.39	L	43	>68	L	0.1	0.1-0.38	N
P07401#	1955	c.209C>G	p.(Ser70*)	DGGE + RA	not	S	12	26	9	no	7	0.063	0.21-0.39	L	56	>68	L	0.05	0.1-0.38	L
P07501#	1943	c.1029+384A>G		DGGE + Sanger	not	S	10	37	24	no		0.07	0.21-0.39	L	40	>68	L	0.11	0.1-0.38	N
P07502#	2011	c.1029+384A>G		Sanger	not	A		8				0.056	0.21-0.39	L	49	>68	L	0.07	0.1-0.38	L
P07503#	1997	c.1029+384A>G		NGS	not	S	25	4	1	no		0.061	0.21-0.39	L	41	>68	L	0.06	0.1-0.38	L
P07504#	1982	c.1029+384A>G		DGGE + Sanger	not	S	17	18	7	no	7	0.032	0.21-0.39	L	40	>68	L	0.04	0.1-0.38	L
P07505#	1981	c.1029+384A>G		DGGE + Sanger	not	S	12	21	24	yes	8	0.049	0.21-0.39	L	52	>68	L	0.04	0.1-0.38	L
P07506#	1967	c.1029+384A>G		Sanger	not	S	20	17	4	yes	3	0.076	0.21-0.39	L	60	>68	L	0.08	0.1-0.38	L

Sample ID	Year of birth	Causal variant	Protein change	Method	c.-21T>C	Symptomatic/Asymptomatic	Age of onset	Age of diagnosis	No. of edemas per year	Long term prophylaxis	Clinical severity score	C1-INH [g/l]	C1-INH Normal values [g/l]	C1-INH evaluation	C1-INH function [%]	C1-INH func. Normal values [%]	C1-INH function evaluation	C4 [g/l]	C4 Normal values [g/l]	C4 evaluation
P07507#	1967	c.1029+384A>G		DGGE + Sanger	not	S	16	32	2	no	2	0.075	0.21-0.39	L	62	>68	L	0.07	0.1-0.38	L
P07508#	1975	c.1029+384A>G		DGGE + Sanger	not	S	17	24	2	no	5	0.071	0.21-0.39	L	78	>68	N	0.06	0.1-0.38	L
P07509#	2012	c.1029+384A>G		Sanger	not	A		5				0.092	0.21-0.39	L	82	>68	N	0.11	0.1-0.38	N
P07510#	1946	c.1029+384A>G		DGGE + Sanger	not	S	21	34	12	no	6	0.034	0.21-0.39	L	31	>68	L	0.02	0.1-0.38	L
P07511#	1993	c.1029+384A>G		DGGE + Sanger	not	A		8		no		0.114	0.21-0.39	L	57	>68	L	0.09	0.1-0.38	L
P07512#	1935	c.1029+384A>G		DGGE + Sanger	not	S	20	21		yes		0.088	0.21-0.39	L	47	>68	L	0.05	0.1-0.38	L
P07601#	1948	c.1396C>T	p.Arg466Cys	DGGE + RA	not	S	18	37	53	yes	8	0.705	0.21-0.39	H	49	>68	L	0.15	0.1-0.38	N
P07602#	1970	c.1396C>T	p.Arg466Cys	DGGE + RA	not	S	5	26	73	yes	10	0.541	0.21-0.39	H	45	>68	L	0.03	0.1-0.38	L
P07603#	1971	c.1396C>T	p.Arg466Cys	DGGE + RA	not	S	6	18	23	yes	9	0.654	0.21-0.39	H	51	>68	L	0.04	0.1-0.38	L
P07701#	1966	c.629T>C	p.Leu210Pro	DGGE + Sanger	not	S	21	31	1	no	5	0.069	0.21-0.39	L	72	>68	N	0.06	0.1-0.38	N
P07702	1986	c.629T>C	p.Leu210Pro	DGGE + RA	not	S	20	20	1	no	3	0.085	0.21-0.39	L	73	>68	N	0.046	0.1-0.38	L
P07801#	1966	c.1396C>T	p.Arg466Cys	DGGE + Sanger	not	S	19	26	9	no	7	0.679	0.21-0.39	H	48	>68	L	0.09	0.1-0.38	L
P07802	1988	c.1396C>T	p.Arg466Cys	Sanger	not	S	5	8	40	yes	10	0.643	0.21-0.39	H	42	>68	L	0.019	0.1-0.38	L
P07803#	1946	c.1396C>T	p.Arg466Cys	DGGE + Sanger	not	S	3	45	14	yes	9	0.694	0.21-0.39	H	65	>68	L	0.14	0.1-0.38	N
P07804	2017	c.1396C>T	p.Arg466Cys	Sanger	not	S	5	0	2			0.212	0.21-0.39	N	21	>68	L	0.21	0.1-0.38	N
P07901#	1985	c.1397G>A	p.Arg466His	DGGE + Sanger	not	S	6	11	1	no	4	0.277	0.21-0.39	N	25	>68	L	0.03	0.1-0.38	L
P07902	1997	c.1397G>A	p.Arg466His	Sanger	not	S	16	4	2	yes	5	0.388	0.21-0.39	N	61	>68	L	0.06	0.1-0.38	L
P07903	2007	c.1397G>A	p.Arg466His	Sanger	not	A		1				0.414	0.21-0.39	H	57	>68	L	0.066	0.1-0.38	L
P07904#	1960	c.1397G>A	p.Arg466His	DGGE + Sanger	not	S	11	29	1	yes	4	0.369	0.21-0.39	N	64	>68	L	0.07	0.1-0.38	L
P07905#	1982	c.1397G>A	p.Arg466His	DGGE + Sanger	not	S	11	14	62	yes	8	0.266	0.21-0.39	N	15	>68	L	0.03	0.1-0.38	L
P07906	2012	c.1397G>A	p.Arg466His	Sanger	not	A		0		no		0.383	0.21-0.39	N	33	>68	L	0.05	0.1-0.38	L
P08001#	1945	c.120_121del	p.(Gly41Argfs*16)	DGGE + NGS	not	S	22	55	1	yes	3	0.055	0.21-0.39	L	62	>68	L	0.04	0.1-0.38	L
P08002#	1970	c.120_121del	p.(Gly41Argfs*16)	DGGE + Sanger	not	S	23	25	1	yes	3	0.026	0.21-0.39	L	21	>68	L	0.02	0.1-0.38	L
P08003#	1968	c.120_121del	p.(Gly41Argfs*16)	DGGE + NGS	not	S	29	27				0.075	0.21-0.39	L	49	>68	L	0.06	0.1-0.38	L
P08101#	1952	c.1397G>A	p.Arg466His	DGGE + Sanger	not	S	26	46	2	yes	6	0.325	0.21-0.39	N	32	>68	L	0.03	0.1-0.38	L
P08201#	1966	c.160del	p.(Leu54Tyrfs*25)	DGGE + Sanger	not	S	30	33	25	yes	5	0.036	0.21-0.39	L	30	>68	L	0.02	0.1-0.38	L
P08202	1986	c.160del	p.(Leu54Tyrfs*25)	DGGE + Sanger	not	S	1	13	86	yes	10	0.055	0.21-0.39	L	43	>68	L	0.04	0.1-0.38	L
P08203	2018	c.160del	p.(Leu54Tyrfs*25)	Sanger	TRANS	S	3	3	17			0.079	0.21-0.39	L	45	>68	L	0.04	0.1-0.38	L
P08301#	1976	c.548T>C	p.Leu183Pro	DGGE + Sanger	not	S	18	21	13	yes	8	0.1	0.15-0.35	L	13	>68	L	0.04	0.1-0.4	L
P08401#	1939	c.1284_1285del	p.(Cys428Trpfs*44)	DGGE + Sanger	not	S	20	58	30	yes	7	0.07	0.15-0.35	L	24	>68	L	0.09	0.1-0.4	L
P08402	1956	c.1284_1285del	p.(Cys428Trpfs*44)	DGGE + Sanger	not	S	20	51	24	yes		0.05	0.15-0.36	L	34	>68	L	0.06	0.14-0.35	L
P08501#	1992	c.650del	p.(Gly217fs*15)	DGGE + Sanger	not	A		9		no		0.03	0.15-0.36	L	25	>68	L	0.02	0.14-0.35	L
P08601	1976	EX1-6del		MLPA	TRANS	S	4	26	16	yes	9	0.06	0.15-0.36	L	38	>68	L	0.04	0.14-0.35	L
P08602	1956	EX1-6del		MLPA	not	S	5	48	10	yes	5	0.06	0.15-0.36	L	45	>68	L	0.05	0.14-0.35	L
P08603	2000	EX1-6del		MLPA	not	S	2	9	6	yes	6	0.04	0.15-0.36	L	29	>68	L	0.03	0.14-0.35	L
P08701	1986	EX1-8del		MLPA	not	S	14	14	12	no	4	0.09	0.15-0.36	L	61	>68	L	0.05	0.14-0.35	L
P08801	1964	EX5-6dup		MLPA	not	S	6	57				0.03	0.15-0.36	L	55	>68	L	0.03	0.14-0.35	L

Table S1: **Czech HAE Patients.** This table presents data on Czech patients diagnosed with Hereditary Angioedema (HAE) and provides the following information in the respective columns. **Sample ID**: Patients from the same family share the first three digits after 'P' in their Sample ID. Probands are distinguished by having a '1' in the last position of the Sample ID. [#] indicates previously published patients. **Causal variant**: The column lists the specific names of the causal variants identified at the cDNA level. **Protein change:** The corresponding alterations in the protein sequence resulting from the causal variants are described. **Method**: The column outlines the detection methods employed to identify the causal variants. The following techniques were used: DGGE - denaturing gradient gel electrophoresis was formerly used for variant screening; NGS - next generation sequencing covering almost the whole *SERPING1* including intronic parts was employed when other methods had not yielded results. MLPA - multiplex ligation-probe amplification was applied to detect large rearrangements; RA - restriction analysis was employed to confirm specific variants, typically in family members of a proband; Sanger - Sanger sequencing of exons and adjacent intronic parts has been the primary method of choice nowadays. **c.-21T>C** column provides information on the presence and form of the variant c.-21T>C in the patient. The following codes are used: not - the variant was not detected in the patient; TRANS - the variant is present in *trans* position to the causal variant; CIS - the variant is present in *cis* position to the causal variant; ND (not determined) - the c.-21T>C variant is present in the patient, but its specific form could not be determined; NA (not available) - DNA not available for an analysis. **Symptomatic/Asymptomatic** column indicates whether the patient is symptomatic (S), asymptomatic (A), or the information is not available (NA). **Age of onset** and **Age of diagnosis** columns contain the patient's age at the time of HAE onset or diagnosis, respectively. **No. of edema per year** column provides attack frequency. When multiple values were available for the patient, the maximum value was used for analysis. **Long term prophylaxis** presents the use of the treatment in the patient. **Clinical severity score**, as introduced by Bygum *et al.* [1], was calculated for each patient with available information on age of onset, attacks location, and long-term prophylaxis usage. Data from the Czech national registry covering the period 2012-2021 was used. **C1-INH [g/l]**, **C1-INH function [%]**, and **C4 [g/l]** indicate the measurements of C1-INH concentration, C1-INH function, and C4 concentration, respectively. These measurements were taken using various methods with different normal values, which are provided for each measurement in their respective columns. When multiple values were available for the patient, the lowest value was used for analysis. **Evaluation** of the measurements is given in the indicated columns using following codes: L – value lower than normal level; N – value within the normal range; H – value higher than normal level. † Patient P00401 carried the missense variant c.1361T>G, along with an in-frame duplication c.564_569dup, which we considered a variant of uncertain significance (VUS). Due to the limited compliance of the patient's family, it was not possible to determine whether the second variant is present in the *trans* or *cis* conformation. Patient P05301 and her daughter P05302 carried the pathogenic frameshift variant c.795_796delGGinsT, along with a VUS variant c.785T>C in cis conformation.

Attack location	**N**
Abdominal	2388
Peripheral	1542
Abdominal + peripheral	603
Facial	560
Laryngeal	314
Other	236
Peripheral + other	146
Peripheral + laryngeal	99
Facial + peripheral	83
Abdominal + other	75
Facial + laryngeal	49
Abdominal + peripheral + other	45
Abdominal + facial	40
Abdominal + laryngeal	29
Abdominal + facial + peripheral	24
Laryngeal + other	22
Abdominal + peripheral + laryngeal	19
Facial + other	13
Peripheral + laryngeal + other	6
Abdominal + facial + laryngeal	6
Facial + peripheral + laryngeal	6
Facial + peripheral + other	4
Abdominal + facial + peripheral + other	3
Abdominal + facial + other	1
Abdominal + peripheral + laryngeal + other	1
Abdominal + laryngeal + other	1
Abdominal + facial + peripheral + laryngeal + other	1
Not known	1

Table S2: **Location of HAE attacks** as they were recorded in 150 HAE patients in the Czech national registry of primary immunodeficiencies.

Treatment	N	
Icatibant (Firazyr®)	3350	62.93%
rhC1-INH (Ruconest®)	799	15.01%
pnfC1-INH (Berinert®)	902	16.95%
nfC1-INH (Cinryze®)	79	1.48%
Attenuated androgens	96	1.80%
Tranexamic acid	88	1.65%
Frozen plasma	8	0.15%
Kallikrein inhibitor	1	0.02%
Total number of treated attacks	5323	

Table S3: **Acute attack treatment.** Fixed drug doses were used in our cohort - Firazyr® (30mg), Ruconest® 2100 U 1-2 vials (median dose 2100 U, range 2100-4200 U), and Berinert® 500 IU 1-2 vials (median dose 1000 IU, range 500-1000 IU). Treatment had to be repeated in 800 attacks. The treatment was evaluated as effective in 98.6% of attacks.

Supplementary Methods

Databases and Bioinformatics

Following population and variant databases and bioinformatic tools have been used to annotate variants and estimate variant impact.

Population databases

Genome Aggregation Database (GnomAD): https://gnomad.broadinstitute.org/ [2]

Variant databases

The Human Gene Mutation Database (HGMD) https://www.hgmd.cf.ac.uk/ [3]

ClinVar: www.ncbi.nlm.nih.gov/clinvar/ [4]

Leiden Open Variation Database (LOVD): https://www.lovd.nl/shared/variants/SERPING1 [5]

Centralized databases for genetics and proteomics

UCSC Genome Browser:https://genome.ucsc.edu/ [6]

Ensembl: http://www.ensembl.org [7]

Uniprot: https://www.uniprot.org/ [8]

In Silico computational prediction tools

Sorting Intolerant From Tolerant (SIFT): http://siftdna.org.submit.html [9]

PolyPhen (version 2): http://genetics.bwh.harvard.edu/pph2/ [10]

CADD: https://cadd.gs.washington.edu/ [11]

Exonic splicing enhancers: ESEfinder release 3.0 [12]

Human Splicing Finder, version 3.1: www.umd.be/hsf [13]

Maximum Entropy (MaxEnt) prediction model (MaxEntScan):
http://hollywood.mit.edu/burgelab/maxent/Xmaxentscan_scoreseq.html [14]

RNA analysis

Total RNA was extracted from the peripheral blood using RiboPure-Blood Kit (Thermo Fisher Scientific). Extracted RNA was reverse transcribed to cDNA with random hexamers using Superscript II (Thermo Fisher Scientific), following the manufacturer's instructions. Subsequent PCR was performed in two steps using Platinum SuperFi DNA polymerase (Thermo Fisher Scientific). Primer sequences are specified below, and reaction conditions are available upon request. Amplicons from the second reaction were checked on 2% agarose gels and characterized by capillary analysis through a commercial service (SeqMe). GeneScan™-1200 LIZ size standard was used for this purpose.

Primers:

1st step PCR:

tag-C1rt-4a	CAGCACCTTTGTGGTTCTCATCGCCAGCCTCCTTACCCAGG
C1rt-4b	AGGGCTGAGAGCCTGTTCCA

2nd step PCR:

FAM-tag	FAM-CAGCACCTTTGTGGTTCTCA
C1rt-4b	AGGGCTGAGAGCCTGTTCCA

Minigene Assay

To investigate the effect of sequence variant on RNA splicing, minigene constructs were created. Wild-type and mutant genomic fragments of SERPING1 comprising exon3 and 229 and 255 bp of flanking upstream and downstream introns were amplified using Platinum Pfx DNA polymerase (Thermo Fisher Scientific). The primer sequences are specified below, and reaction conditions are available upon request. PCR products were cloned into the multiple cloning sites inside the pET01 vector (MoBiTec) using restriction enzymes ApaI and SmaI.

HepG2 cells (European Collection of Authenticated Cell Cultures), maintained in RPMI 1640 medium (Sigma-Aldrich) supplemented with 10% foetal bovine serum (Sigma-Aldrich), were seeded (2×105 cells per transfection) into a 12-well plate 1 day prior to transfection. The cells were transfected using 500 ng of minigene construct and 2.4µl of transfection reagent XtremeGene 9 (Roche). RNA was extracted 24 h after transfection using a Quick-RNA Miniprep Kit (Zymo Research), and subsequently, RT-PCR was performed. Reverse transcription was performed using SuperscriptTM II reverse transcriptase (Thermofisher Scientific) according to the manufacturers' protocol. Subsequent PCR for capillary electrophoresis was performed using Taq DNA polymerase (Thermofisher Scientific) and fluorescently labelled primer pET1A-FAM.

Primers:

PCR - capillary analysis

pET1A-FAM	CAGCACCTTTGTGGTTCTCA
rPET_PS02	GCACTGATCCACGATG

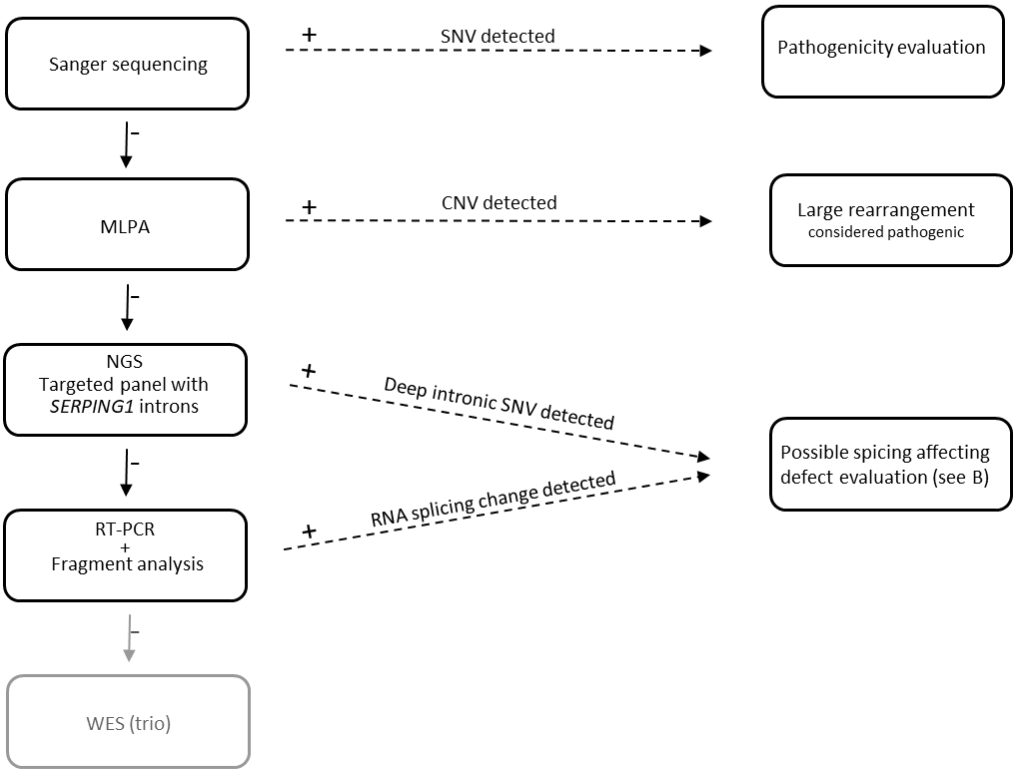
SERPING1 cloning

f_C1e3_clon_ApaI	GGGCCCTTCTGCAGAGCACATTCCTGT
r_C1e3_clon_SmaI	CCCGGGGGTTAGTGGCTGCGACCTTA

SERPING1 mutagenesis

f_C1e3_c.550+3A>G_mut	ccaggtcctgctcggtgagaccctgc CCAGGTCCTGCTCGGTGAGACCCTGC
r_C1e3_c.550+3A>G_mut	GCAGGGTCTCACCGAGCAGGACCTGG

a Standard variant detection and evaluation



b Possible splicing defect evaluation

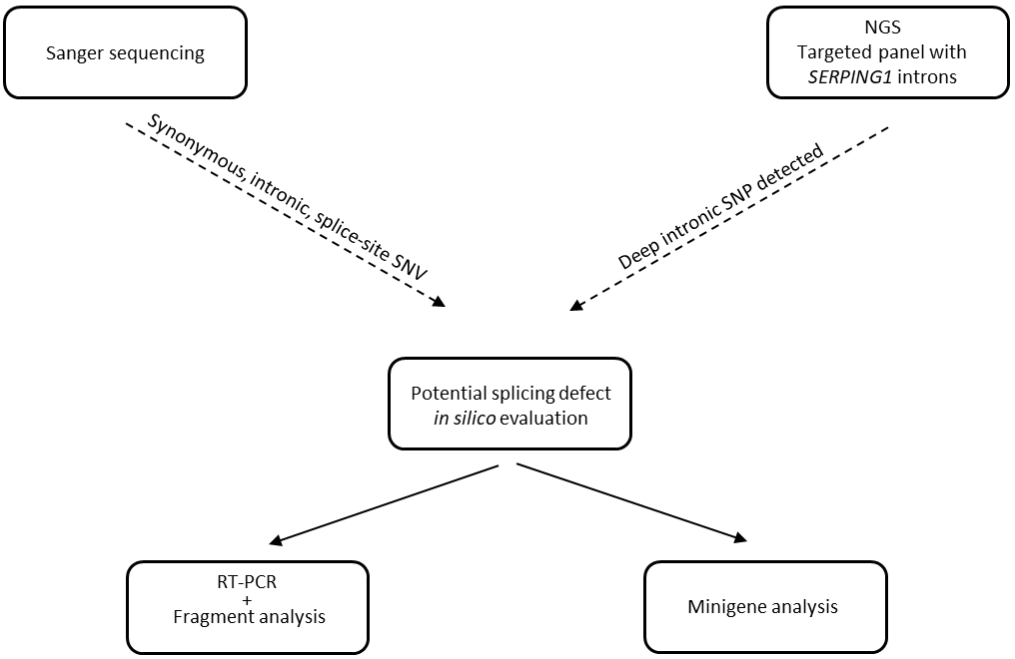


Fig. S1: The current workflow for screening pathogenic variants in SERPING1.'+' indicates the presence of a detected variant, while '-' indicates its absence. Solid line arrows represent the procedural steps, while hatch-marked arrows indicate the need for pathogenicity evaluation of the detected variant. **a** Standard variant detection and evaluation. Initially, Sanger sequencing is performed on exonic and adjacent intronic regions. If no potentially pathogenic variant is identified, MLPA is conducted. Two methods are employed to screen for splicing and deep intronic defects: Targeted NGS and RT-PCR with fragment analysis. Targeted NGS covers almost all intronic regions of SERPING1 and enables the detection of copy number variations (CNVs). Although the MLPA step could theoretically be omitted, it is typically performed due to its speed and efficiency in CNV detection. Concurrently, RNA analysis by RT-PCR is sometimes performed if patient RNA can be obtained promptly. Finally, in one case where no pathogenic variant was detected by previous methods, WES analysis is currently performed on the patient and their parents. While the pathogenicity of null variants is often clear, further evaluation is required for missense and splicing variants. **b** Possible splicing defect evaluation. If RT-PCR analysis has not been performed during the standard evaluation, a set of RT-PCRs with primers located inside exons, followed by fragment analysis, is conducted. In parallel with the RT-PCR analysis, or as an alternative in cases where patient RNA is not available, minigene analysis is utilized.

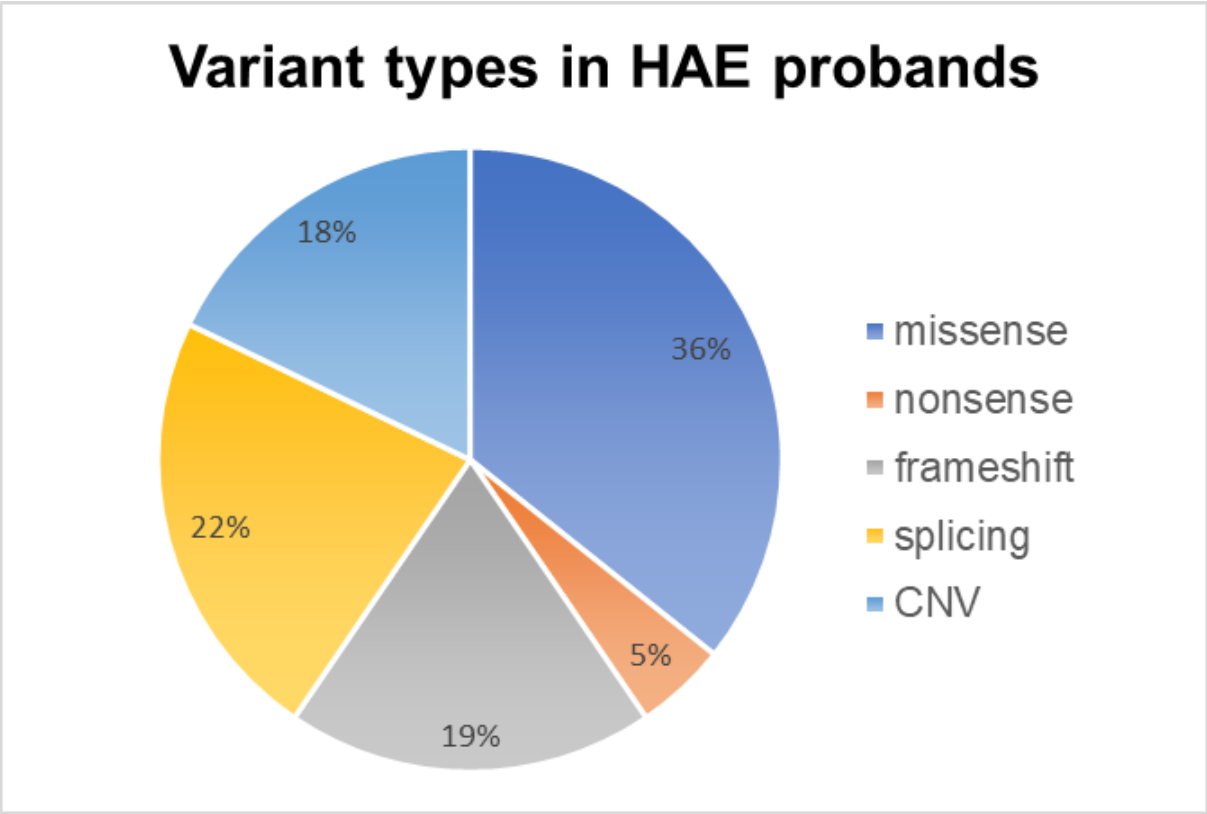


Fig. S2: Proportions of probands with indicated causal variant type in our cohort. The proportions of probands with detected causal variant types were calculated from 84 out of 85 pedigrees in our cohort. In one case, no causal variant was identified. The overall SERPING1 variants comprise missense variants (36%; Table 2) listed in Table 2, nonsense variants (5%; Table 3) and frameshift variants (19%; Table 4), splicing defects (22%; Table 5) and large deletions and duplications (18%; Table 6) amounting to a total of 56 distinct variants and including 5 novel variants.

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