

FIG E1. WB analysis of variants N272del and K273del before and after treatment with glycosidases. Before treatment, K273del (lane 3) has a slightly higher M_r compared with N272del (lane 2). After treatment, WB demonstrates that N272del (lane 5) and K273del (lane 6) have the same M_r . Human purified C1-INH was used as a positive control (lane 7, before treatment; lane 8, after treatment). Deglycosylation mix contains Peptide-N-Glycosidase F (PNGase F), O-glycosidase, neuraminidase, β 1-4-galactosidase S, and β -N-acetylhexosaminidase. It removes both N-linked and "simple" O-linked glycans.

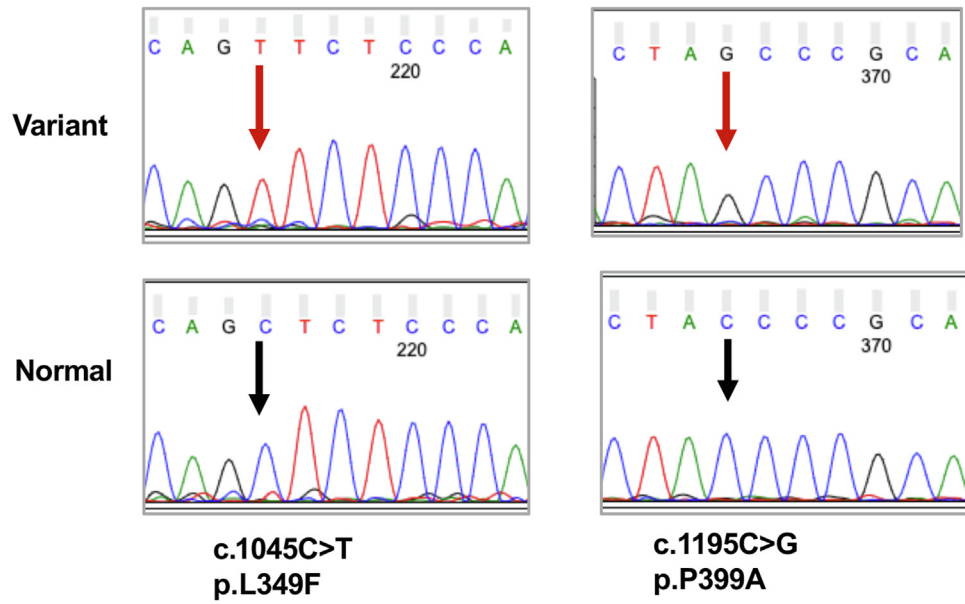


FIG E2. SGS confirms that the variants c.1045C>T (p.L349F) and c.1195C>G (p.P399A) are located on different alleles.

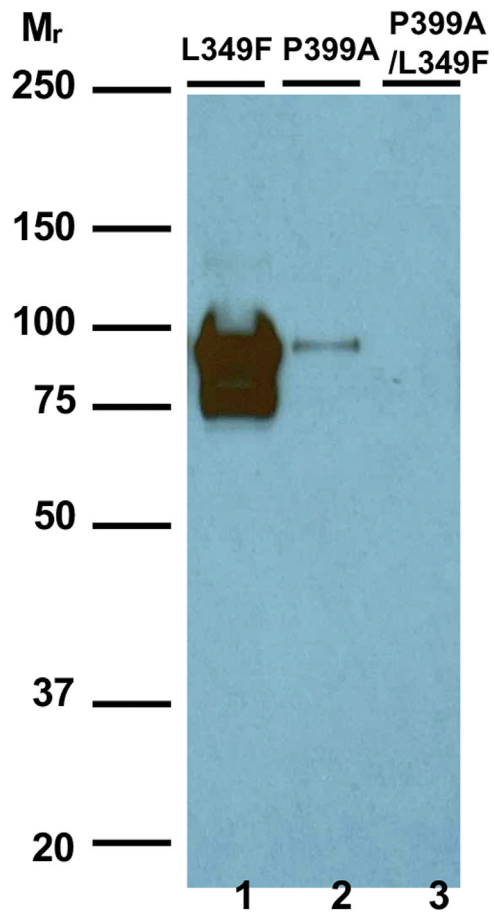


FIG E3. Recombinant expression of C1-INH variants L349F, P399A, and L349F/P399A double mutants in nonreducing condition. L349F has normal secretion compared with that of WT (not shown). P399A and L349F/P399A were barely secreted.

TABLE E1. Medications approved for the treatment of HAE

Medication (trade name)	HAE medication list			Patient response (patient no.)										
	Mechanism of action	Prophylaxis	On demand	504 I224S	601 N272del	1201 K273del	1301 K273del	701 P399A	702 L349F/P399A	801 F471C		901	1001	1101
Plasma-derived C1-INH (Cinryze)	C1-INH (human) concentrate, IV	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Plasma-derived C1-INH (Berinert)	C1-INH (human) concentrate, IV	Yes	Yes	Yes	NA	Yes	NA	NA	NA	NA	NA	NA	NA	NA
Plasma-derived C1-INH (Haegarda)	C1-INH (human) concentrate, SC	Yes	No	NA	NA	Yes	NA	NA	NA	NA	Yes	NA	NA	NA
Recombinant C1-INH (Ruconest)	C1-INH (recombinant) concentrate, IV	No	Yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Fresh frozen plasma*	Contains C1-INH, IV	No	Yes	No	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lanadelumab (Takhzyro)	mAb kallikrein inhibitor, SC	Yes	No	NA	Yes	NA	Yes	NA	NA	NA	NA	Yes	Yes	Yes
Ecallantide (Kalbitor)	Recombinant kallikrein inhibitor, SC	No	Yes	NA	NA	ANA†	NA	NA	NA	NA	ANA‡	NA	NA	NA
Bertralstat (Orladeyo)	Plasma kallikrein inhibitor, oral	No	Yes	NA	NA	NA	NA	NA	NA	NA	No	No	NA	NA
Icatibant (Firazyr)	Bradykinin receptor antagonist, SC	No	Yes	NA	Yes	No	No	Yes	Yes	Yes	No	No	Yes	Yes

ANA, Anaphylaxis; IV, intravenous; NA, not applicable.

*Fresh frozen plasma is a second-line therapy in the acute treatment of laryngeal attacks and severe gastrointestinal attacks if first-line therapies are not available.

†After the administration of ecallantide, patient 1201 developed flushing, dyspnea, and loss of consciousness within a few minutes.

‡The patient developed an anaphylactic reaction consisting of chills, dyspnea, and paleness within minutes after receiving the ninth dose of ecallantide.