

Summary of polymerase acidic protein (PA) amino acid substitutions assessed for their effects on PA inhibitor (PAI) baloxavir susceptibility*

Type/subtype	Amino acid substitution	Baloxavir susceptibility by phenotypic assay (EC ₅₀ fold-change) ^a	Source of viruses ^b	References
A(H1N1)	E23K	5	RG	(1)
	A36V	4	RG	(1)
	I38F	8–11	RG	(1)
	I38L	6	RG	(2)
	I38M	13	RG	(1)
	I38N	24	RG	(2, 3)
	I38S	12	RG	(2)
	I38T	22–54	RG; Cell/BXA	(1, 4, 5)
	I38V	2	RG	(1)
	E119D	7	RG	(1)
	E198K	3	RG	(6)
A(H1N1)pdm09	E23G	4–7	Sur; RG	(7–10)
	E23K	7–13	Sur/No; RG	(9–11)
	E23R	13	RG	(12)
	K34R	2–5	Sur	(9)
	A37T	5	Sur/BXA	(13)
	I38F	7–17	RG	(14, 15)
	I38L	7–12	Sur/No	(7, 8, 16, 17)
	I38M	7–9	RG; Mice/BXA	(14, 15, 18)
	I38S	31–112	Cell/BXA; Clin/BXA; Sur/BXA	(9, 11, 16, 19)
	I38T	11–124	RG; Cell/BXA; Clin/BXA; Sur/BXA	(9, 11, 14–16, 20, 21)
	I38V	2–4	Sur/No	(7, 9)
	E198K	2	RG	(6)
	E199D	3	RG	(17)
	E199G	1–4	Mice/BXA; Sur	(9, 18)
A(H3N2)	L28P	1–3	RG; Sur	(1, 9)
	E23G ^c	2–3	RG	(2, 3, 10)
	E23K	6	RG	(1, 10)
	E23R	19	RG	(12)
	K34R	4	Sur	(9)
	A36V	6	RG	(1)
	A37T	8	RG	(1)
	I38F	16–20	RG	(1, 14, 15)
	I38L	2–8	RG; Sur	(2, 9)
	I38M	4–24	RG; Sur/No; Sur/BXA	(1, 3, 7–9, 14–16)
	I38N	10	RG	(2)
	I38S	6	RG	(2)
	I38T	20–14	RG; Clin/BXA; Cell/No; Sur/BXA; Sur/No	(1, 3, 9, 15, 16, 19–26)
	I38V	1–2	RG; Sur/No	(1, 7)
	E119D	5	RG	(1)
	E198K	6	RG	(6)
	E199G	5	RG	(1)
B	E23K	1–3	RG	(1, 27)
	M34I	1	Sur	(9)
	F36V ^d	1	RG	(1)
	I38F	2–8	RG	(1, 15)

	I38M	2–8	RG	(1, 14, 15, 27)
	I38T	5–15	RG	(1, 14, 15, 27)
	I38V	1–2	Sur/No	(7, 9)
	E120D ^c	2-3	RG	(1, 28)
	G199R	2	RG	(17)

* Additional amino acid substitutions in PA, which conferred no change in baloxavir susceptibility, were investigated in references #1 (Omoto S et al., 2018) and #2 (Hashimoto T et al., 2020).

^a Assessed by cell culture-based assays (focus, plaque or yield reduction assays, high-content imaging neutralization (HINT) and ViroDot assay). EC₅₀ fold-change was calculated compared to matched control virus or type/subtype-specific median EC₅₀.

^b Cell, Cell culture; Clin, Clinical trial; Mice, mouse model; RG, Reverse Genetics; Sur, Surveillance studies; BXA, Substitution selected under baloxavir pressure; No, baloxavir not used.

^c E23G in A(H3N2) subtype was detected in a baloxavir-treated patient in a clinical trial (T0831). RG virus with E23G was tested by phenotypic assay.

^d Corresponds to A36V in influenza type A PA.

^e Corresponds to E119D in influenza type A PA.

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