

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

Type/subtype	Amino acid substitution	Baloxavir susceptibility by phenotypic assay ^a IC ₅₀ fold-change	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)
A(H1N1)pdm09	E23G	4-7	Sur/No	(6, 7)
	E23K	7-9	Sur/No	(8)
	I38F	7-17	RG	(9, 10)
	I38L	7-9	Sur/No	(6, 7, 11)
	I38M	7-29	RG; Mice/BXA	(9, 10, 12)
	I38S	31-112	Cell/BXA; Clin/BXA; Sur/BXA	(8, 11, 13)
	I38T	44-124	RG; Cell/BXA; Clin/BXA; Sur/BXA	(8-11, 14, 15)
	I38V	2-3	Sur/No	(6)
	E199G	1	Mice/BXA	(12)
A(H3N2)	L28P	3	RG	(1)
	E23G	2-3	RG	(2, 3)
	E23K	6	RG	(1)
	A36V	6	RG	(1)
	A37T	8	RG	(1)
	I38F	16-20	RG	(1, 9, 10)
	I38L	2	RG	(2)
	I38M	4-21	RG; Sur/No	(1, 3, 6, 7, 9-11)
	I38N	10	RG	(2)
	I38S	6	RG	(2)
	I38T	20-391	RG; Clin/BXA; Cell/No; Sur/BXA; Sur/No	(1, 3, 10, 11, 13-20)
	I38V	1-2	RG; Sur/No	(1, 6)
	E119D	5	RG	(1)
	E199G	5	RG	(1)
B	E23K	1-3	RG	(1, 21)
	F36V ^c	1	RG	(1)
	I38F	2-8	RG	(1, 10)
	I38M	2-8	RG	(1, 9, 10, 21)
	I38T	5-15	RG	(1, 9, 10, 21)
	I38V	1-2	Sur/No	(6)
	E120D ^d	2	RG	(1)

* Additional amino acid substitutions in PA, which conferred no change in baloxavir susceptibility, were investigated by Omoto S et al., 2018 and Hashimoto T et al., 2020.

^a Assessed by cell culture-based assays (focus, plaque, or yield reduction assay, high-content imaging neutralization (HINT) and ViroDot assay). IC₅₀ fold-change was calculated by comparing to control virus or (sub)type-specific median IC₅₀.

^b Cell, cell culture; Clin, clinical trial; Mice, mouse model; RG, reverse genetics; Sur, surveillance studies; /BXA, substitution selected in the presence of baloxavir; /No, baloxavir was not used.

^c Corresponds to A36V in PA of influenza A viruses.

^d Corresponds to E119D in PA of influenza A viruses.

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