Table S2. List of residues identified as possibly involved in changing the pathogenicity, virulence or fitness of IAVs

Encoding protein – amino acid position	Effect described in literature	References
PB2-9	D9N increases virulence	[1, 2]
PB2-45	Impacts thermo-sensitive phenotype	[3]
PB2-158	E158K/G increase pathogenicity of H4N6 and H1N1pdm viruses	[4-6]
PB2-199	199S increases pathogenicity of H5N1 in mice	[2, 5, 7, 8]
PB2-251	R251K increases replication and pathogenicity	[9, 10]
PB2-253	D253N increases pathogenicity	[5, 11, 12]
PB2-265	N265S thermo-sensitive phenotype	[13-15]
PB2-271	T271A increases polymerase activity	[5, 7, 16]
PB2-339	K339T modulates polymerase activity and virulence	[17]
PB2-368	368K increases pathogenicity when combined with PB2-627K	[18]
PB2-431	M431I reduces Pimodivir susceptibility and virulence	[19, 20]
PB2-478	V478L thermo-sensitive phenotype	[14, 21]
PB2-504	Interacts with residue PA-550 in RNAP II degradation	[22]
PB2-588	T588I increases virulence	[7, 8, 23]
PB2-590	S590 compensates mutation PB2-E627K with PB2-R591	[5, 24, 25]
PB2-591	Q591R/K increases pathogenicity and compensates mutation PB2-E627K	[5, 24-26]
PB2-627	Major determinant of transcription / replication efficiency E627K increases pathogenicity of H4N6 but attenuates swine H3N2	[5, 6, 8, 27-30]
PB2-685	increases virulence when combined mutation in HA-190 or HA-212	[31]
PB2-701	D701N compensates effect of mutation PB2-E627K and enhances replication and pathogenicity of H1N1pdm and $H1_{av}N1$ viruses	[5, 9, 32, 33]
PB2-714	714R increases the cap-binding efficiency of PB2 when combined with PB2-701N	[5]
PB1-27	D27N increases polymerase activity	[34]
PB1-180	G180E enhances virus growth kinetics	[35]
PB1-181	I181T increases virulence of H5N2 in mice	[36]
PB1-216	S216G enhances virus growth kinetics and virulence	[35, 37]
PB1-229	K229R reduces favipiravir susceptibility and viral fitness	[19]
PB1-265	K265N attenuates virus	[14]
PB1-353	K353R impacts virulence	[38]
PB1-361	S361R enhances virus growth kinetics	[35]
PB1-391	K391E increases virus temperature sensitivity	[13-15]
PB1-456	H456Y plays a role in virulence and adaptation in mice	[39]
PB1-469	A469T enhances replication, pathogenicity and transmission	[40]
PB1-473	V473 increases polymerase activity, L473 decreases polymerase activity in H1N1pdm virus	[5, 41]
PB1-566	T566A could impact virulence	[38]

PB1-581	E581G increases virus temperature sensitivity	[13, 15]
PB1-591	V591I attenuates virus	[14]
PB1-598	Increase polymerase activity	[5, 41]
PB1-621	Q621R could enhance virus growth kinetics	[35]
PB1-653	P653L increases polymerase activity	[19]
PB1-654	N654S could enhance virus growth kinetics	[35]
PB1-661	A661T increases virus temperature sensitivity	[13-15]
PB1-F2-51	T51M decreases lethality	[42]
PB1-F2-56	V56A decreases lethality	[42]
PB1-F2-62	L62: impacts inflammatory activity and enhanced pathogenicity of bacterial superinfection /P62: impacts antimicrobial activity	[42-44]
PB1-F2-66	N66S increases virulence in mice with limited effect in H1N1pdm virus 66S enhances pathogenicity of bacterial superinfection	[44-46]
PB1-F2-68	68I : responsible for promotion of the peptide's cytotoxicity and permeabilization of the mitochondrial membrane (in combination with PB1-F2-69L and -70V)	[47]
PB1-F2-69	69L: responsible for promotion of the peptide's cytotoxicity and permeabilization of the mitochondrial membrane (in combination with PB1-F2-68I and -70V)	[47]
PB1-F2-70	70V: responsible for promotion of the peptide's cytotoxicity and permeabilization of the mitochondrial membrane (in combination with PB1-F2-68I and -69L)	[47]
PB1-F2-79	R79: impacts inflammatory activity and enhances pathogenicity of bacterial superinfection /Q79: impacts antimicrobial activity	[7, 42-44]
PB1-F2-82	L82: Impacts inflammatory activity and enhances pathogenicity of bacterial superinfection /S82: impacts antimicrobial activity	[7, 42-44]
PB1-F2-87	E87G decreases lethality	[7]
PA-85	85I enhances activity of the Cal polymerase	[48]
PA-129	I129T enhances replication, pathogenicity and transmission	[40]
PA-142	142N increases pathogenicity of H5N1 in mice, 142E affects pathogenicity when combined with PB2-627K	[2, 21]
PA-224	Affects endonuclease activity S224P highly virulent phenotype of H5N1 in duck	[49, 50]
PA-295	L295P is responsible for transcription and replication activity	[51]
PA-298	E298K contributes to virulence	[52]
PA-336	336M increases avian polymerase activity in mammals cells	[5, 48]
PA-343	A343T increases H1N1pdm virulence	[8, 38]
PA-383	N383D highly virulent phenotype of H5N1 in duck	[21, 50]
PA-409	S409N increases transmissibility of H1N1pdm virus	[7, 8]
PA-421	421I increases pathogenicity of H5N1 in mice	[2, 18, 21]
PA-552	552S increases polymerase activity	[5, 7, 8, 53]
PA-615	615N increases polymerase activity	[5]
PA-666	L666F reduces polymerase activity	[19]
PA-713	H713R defects packaging	[54]
PA-714	A714G defects packaging	[54]
NP-16	G16D increases MxA resistance	[7, 8, 55]

NP-34	34G increases temperature sensitivity	[13]
NP-41	41V enhances polymerase activities and replication of H7N9	[56]
NP-48	affectes MxA resistance	[57]
NP-53	53D increases MxA resistance	[55]
NP-64	D64G increases thermosensitivity of strains	[13]
NP-72	D72A affects incorporation of vRNAs into VLPs	[58]
NP-74	R74A affects incorporation of vRNAs into VLPs	[58]
NP-98	affects MxA resistance	[21, 57]
NP-99	affects MxA resistance	[57]
NP-100	100I/V increases MxA resistance	[7, 8, 55]
NP-101	D101G contributes to virulence	[28, 51]
NP-108	Thermos-sensitive phenotype	[3]
NP-109	I109T increases replication in chicken	[7, 8, 59]
NP-113	K113A affects incorporation of vRNAs into VLPs	[58]
NP-150	R150A affects viral-genome replication and transcription	[58]
NP-156	R156A affects incorporation of vRNAs into VLPs	[58]
NP-174	R174A affects incorporation of vRNAs into VLPs	[58]
NP-175	R175A affects incorporation of vRNAs into VLPs	[58]
NP-188	T188 regulates viral replication by controlling NES2-dependent NP nuclear export and the polymerase activity of the vRNP complex	[60]
NP-195	R195A affects incorporation of vRNAs into VLPs	[60]
NP-199	R199A affects incorporation of vRNAs into VLPs	[60]
NP-204	S204 requires for NP binding to viral polymerase	[61]
NP-207	W207 requires for NP binding to viral polymerase	[61]
NP-208	R208A affects viral-genome replication and transcription	[58, 61]
NP-210	210D enhances polymerase activities and replication of H7N9	[56]
NP-213	R213A affects viral-genome replication and transcription	[58]
NP-214	Involves in the conversion of filamentous virions into spherical virions	[7, 8, 62]
NP-217	Involves in the conversion of filamentous virions into spherical virions	[21, 62, 63]
NP-239	M239L thermos-sensistive lesion	[64]
NP-253	Involves in the conversion of filamentous virions into spherical virions	[62]
NP-254	E254A affects viral-genome replication and transcription	[58]
NP-260	A260R affects viral-genome replication and transcription	[58]
NP-273	K273A affects viral-genome replication and transcription	[58]
NP-283	L283P increases MxA resistance	[7, 8, 55]
NP-289	289H increases MxA resistance	[55]
NP-305	305K increases MxA resistance	[7, 8, 28, 55]
NP-313	F313Y/V increases MxA resistance	[7, 8, 55]
NP-316	316M increases MxA resistance	[55]
NP-319	N319K enhances viral replication	[5]
NP-325	K325A affects incorporation of vRNAs into VLPs	[58]
NP-337	A337R affects viral-genome replication and transcription	[58]
NP-343	NP-V343L mutation switched from being highly BNP-sensitive to moderately BNP-resistant	[65]
NP-350	350K increases MxA resistance	[55]

NP-351	351K increases MxA resistance	[55]
NP-353	353I/S increases MxA resistance	[21, 28, 55]
NP-355	R355A affects viral-genome replication and transcription	[58]
NP-357	Q357K increases MxA resistance and virulence affects also the pathogenicity when associated to PB2-627K	[7, 8, 55, 66]
NP-361	R361A affects incorporation of vRNAs into VLPs	[58]
NP-387	A387R affects viral-genome replication and transcription	[58]
NP-405	Q405A affects viral-genome replication and/or transcription	[58]
NP-412	F412A affects viral-genome replication and/or transcription	[58]
NP-488	F488A affects viral-genome replication and/or transcription	[58]
NP-489	F489A affects viral-genome replication and/or transcription	[58]
M1-30	Influences the morphology of virions	[62]
M1-41	P41A alters virion morphology, reducing the number and length of filamentous virions, as well as reducing the neuraminidase activity of virions	[67]
M1-90	P90 inhibes ribonucleoproteins transcription	[68]
M1-95	R95K described in pathogenic strains of H5N1	[69]
M1-101	R101S affects viral replication and thermo-sensibility	[70]
M1-105	R105S affects viral replication and thermo-sensibility	[70]
M1-108	T108 inhibes ribonucleoproteins transcription	[68]
M1-132	Role in nuclear import	[71]
M1-142	Impacts morphology of virions	[72]
M1-207	Impacts morphology of virions	[72]
M1-209	Impacts morphology of virions	[72]
M1-224	N224S described in pathogenic strains of H5N1	[69]
M1-230	R230K described in pathogenic strains of H5N1	[69]
M2-55	C55F increases transmissibility	[18]
NS1-18	V18A thermo-sensitive phenotype	[73]
NS1-35	R35 and R46 critical for binding to and blocking activation of PKR and for efficient virus propagation	[74]
NS1-38	critical role in RNA binding and inhibition of IFN production	[75]
NS1-42	P42S increases virulence in mice S42D attenuates virulence	[76-78]
NS1-44	R44K thermo-sensitive phenotype	[73]
NS1-46	R35 and R46 critical for binding to and blocking activation of PKR and for efficient virus propagation	[74]
NS1-48	S48A/D affects virus replication	[78]
NS1-55	K55E, K66E, and C133F restored ability to conteract interferon response	[79]
NS1-64	I64T affects interferon response and virulence	[80]
NS1-66	K55E, K66E, and C133F restored ability to conteract interferon response	[79]
NS1-92	E92 increases clinical signs	[8]
NS1-97	E97A decreases TRIM25 activity	[81]
NS1-103	F103L increases virulence F103 critical for CPSF binding	[82-84]
NS1-106	M106I increases virulence M106 critical for CPSF binding	[82-84]
NS1-123	Suspected to have a role in human adaptation, and virulence	[49, 85]

NS1-133	K55E, K66E, and C133F restore ability to conteract interferon response	[79]
NS1-149	A149 antagonizes interferon production and increases pathogenicity of H5N1 in chicken	[86]
NS1-171	A171Y increases NS1 expression and reduces IFN expression	[87, 88]
NS1-195	S195P thermo-sensitive phenotype	[73]
NS1-200	N200S increase virulence of H5N1 in ferret, enhanced IFN 1 activity	[89]
NS1-205	N205K enhanced replication, pathogenicity and transmission G205R increase virulence of H5N1 in ferret, enhanced IFN 1 activity	[40, 89]
NS1-215	T215A attenuates viral replication	[18, 28, 78]
NEP-47	T47A increases virulence of H5N1 in ferret	[89]
NEP-48	T48N enhances replication, pathogenicity and transmission	[40]
NEP-51	M51I increases virulence of H5N1 in ferret	[89]
NEP-69	E69G increases virulence H5N2 in mice	[36]

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