

Supplemental Table S4. Viral genetic variations potentially associated with clinical groups.

HSV-2 Gene: Variation	Clinical Group (Isolates w/ Variation)	Predicted effect[^]	Protein Function	Neurovirulence
gK (UL53): V323M	All CSF Isolates (CNS11, DISS14)	Loss of one TM domain	Glycoprotein at virion and cell surface; interacts with gB and UL20 (1); important for cytoplasmic envelopment, viral egress, and virus-induced cell fusion	gK null virus exhibits poor neuronal spread in culture including decreased retrograde and anterograde transport (2); reduced spread within eye and to nervous system, as well as increased survival, following ocular challenge in mice (3)
gI (US7): R159L + P215S	All CSF Isolates (Both: CNS11, DISS14 <u>R159L only:</u> CNS03, SEM13, CNS15*, DISS29* <u>P215S only:</u> CNS15*, DISS29)	R159L: adds one TM domain; P215S: no change	Glycoprotein at virion and cell surface; forms heterodimer with gE to form viral Fc receptor (4); required for cell-to-cell spread of virus in epithelial and neuronal cells (5, 6);	gI null virus exhibits poor neuronal spread in culture; reduced spread in retina and to retinorecipient areas of the brain following ocular challenge in mice (6)
UL8: R221S	All CSF Isolates (CNS11, DISS14)	No predicted change	Putative primase subunit of helicase primase complex; required for unwinding of viral DNA	None identified
US2: F137L	All CSF Isolates (CNS11, DISS14)	No predicted change	Tegument protein; binds and phosphorylates TAK1 to positively regulate NFkB signaling (7)	Virus containing mutated US2 forms small plaques in culture (8); Mutant virus containing a deletion of both US2 and PK result in decreased death following intracerebral injection in mice (9)
gG (US4): R338L, S442P, E574D	All CSF Isolates (CNS11, DISS14)	No predicted change	Binds and enhances function of chemokines (10); enhances neurotrophin-dependent axonal growth in culture (11)	Virus containing mutated gG results in decreased death following intracerebral injection in mice (8)
UL24: V93A	No CNS Isolates; only found in SEM isolates (SEM02, SEM13, SEM18)	No predicted change	Membrane-associated nuclear protein; associated with dispersal of nucleolin during infection (12, 13)	UL24 null virus forms small plaques in culture (14); decreased viral load in eye and nervous system following ocular challenge in mice (15–17)
UL20: P129L	All DISS Isolates w/ CNS Involved (DISS14, DISS29)	Change in position of three TM domains	Membrane-associated protein interacts with gK and gB (1); required for gK glycosylation, cell surface expression (18), and virus-induced cell fusion (19); important for viral egress (20)	UL20 null virus forms small plaques in culture (19); RNA inhibition of UL20 results in decreased rates of encephalitis following HSV footpad infection in mice (21)

* present as minor variant

[^] Prediction by SMART Analysis

References for Supplemental Table S4

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