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Sean Stout
Children’s Mercy Hospital, sstout@cmh.edu

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Herpes simplex virus whole genome sequencing for antiviral resistance in a child with DOCK8 deficiency and chronic infection

**Submitting/Presenting Author (must be a trainee):** Sean Stout, MD  
**Primary Email Address:** sstout@cmh.edu

**Resident**

**Primary Mentor (one name only):** Dwight Yin, MD  
**Other authors/contributors involved in project:**  
Sean C. Stout¹, Alexander L. Greninger², Rangaraj Selvarangan³⁴⁸, Alexandra F. Freeman⁵, Brandon D. Newell⁶⁷, Erin D. Stahl⁴⁷, Dwight E. Yin⁴⁸  
¹Department of Pediatrics, Children’s Mercy, Kansas City, MO  
²Department of Laboratory Medicine, University of Washington School of Medicine, Seattle, WA  
³Department of Pathology and Laboratory Medicine, Children’s Mercy, Kansas City, MO  
⁴School of Medicine, University of Missouri-Kansas City, Kansas City, MO  
⁵Laboratory of Clinical Immunology and Microbiology; National Institute of Allergy and Infectious Diseases; National Institutes of Health, Bethesda, MD  
⁶Division of Dermatology, Department of Pediatrics, Children’s Mercy, Kansas City, MO  
⁷Section of Ophthalmology, Department of Surgery, Children’s Mercy, Kansas City, MO  
⁸Division of Infectious Diseases, Department of Pediatrics, Children’s Mercy, Kansas City, MO

**Describe role of Submitting/Presenting Trainee in this project (limit 150 words):** Personally cared for patient throughout various hospitalizations. Performed extensive chart review focusing on patient presentation, various treatments, response to treatments, and viral testing. Created charts to correlate antiviral treatments with antiviral resistance demonstrated on phenotypic and genotypic resistance tests. Helped formulate and write abstract.

**Background, Objectives/Goal, Methods/Design, Results, Conclusions limited to 500 words**

**Background:**  
Patients with dedicator of cytokinesis 8 (DOCK8) deficiency are prone to severe, recurrent or chronic mucocutaneous herpes simplex virus (HSV) infections that may develop antiviral resistance. We present the case of a child with DOCK8 deficiency and chronic, resistant HSV-1 mucocutaneous infections to illustrate the potential clinical utility of an investigational viral whole genome sequencing approach to detecting active and latent HSV resistance mutations longitudinally.

**Methods/Design:**  
We abstracted clinical and laboratory data in a 14 year old boy with DOCK8 deficiency with repeated viral culture growth of HSV-1. HSV-1 DNA from seven positive viral culture specimens collected during 2015-
2018 were sequenced on an Illumina® MiSeq to >150X depth. Consensus genomes were called using an established HSV genome pipeline, and reads were mapped to the HSV-1 strain reference genome (NC_001806). Sequence variants were checked against an online database of UL23 (thymidine kinase) and UL30 (DNA polymerase) variants associated with antiviral resistance.

**Results:**
The patient had low CD4+ T cells (initial 248 cells/mm³), eosinophilia, elevated IgE (initial 9660 kU/L), severe eczematous dermatitis, chronic obstructive and interstitial lung disease, growth delay, and presented with recurrent infections including *Staphylococcus aureus*, *Candida albicans*, JC virus, and HSV-1. He was receiving prophylaxis with subcutaneous immunoglobulin G, trimethoprim-sulfamethoxazole, and acyclovir. Family declined hematopoietic stem cell transplantation. Mucocutaneous HSV-1 infections extensively involved his face, trunk, and extremities with more severe infections involving his cornea, lips, perineum, scalp, and periorbital regions. Scalp and periorbital lesions were proliferative and edematous papules and plaques consistent with HSV vegetans (Figures 1-2) and confirmed by scalp biopsy. Although early HSV-1 infections responded to oral or IV acyclovir, clinical response decreased over time, requiring advancement of therapies to high-dose acyclovir IV, foscarnet IV, cidofovir IV, topical cidofovir cream, and/or interferon-alpha with variable clinical response.

Phenotypic testing detected acyclovir resistance in HSV isolated from four samples while the patient was on acyclovir and no resistance in a sample while not on acyclovir. Phenotypic foscarnet resistance was detected in one sample without prior patient exposure to foscarnet. Viral whole genome sequencing detected the UL23 variant R176Q (associated with acyclovir resistance) on all specimens, whether on acyclovir or not, and the UL30 variant T821M (associated with acyclovir and cidofovir resistance) only when on cidofovir. When phenotypic testing and genome sequencing were discordant, clinical response appeared to be more consistent with genome sequencing results.

**Conclusions:**
This patient with DOCK8 deficiency illustrates the potential severity of chronic, resistant mucocutaneous HSV-1 infection. Viral genome sequencing for antiviral resistance mutations may provide additional information about the presence of clinically significant variants, which may result from detecting smaller or latent HSV-1 sub-populations.
**Figure 1.** HSV vegetans of the right parieto-occipital scalp in patient with DOCK8 deficiency.
Figure 2. Left periorbital HSV vegetans in patient with DOCK8 deficiency.