Viral Whole Genome Sequencing for Antiviral Resistance in a Child with DOCK8 Deficiency and Recurrent HSV-1

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Viral Whole Genome Sequencing for Antiviral Resistance in a Child with DOCK8 Deficiency and Recurrent HSV-1

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Background
- Patients with dedicator of cytokinesis 8 (DOCK8) deficiency are prone to severe recurrent or chronic mucocutaneous herpes simplex virus (HSV) infections
- HSV strains may develop antiviral resistance over time
- We present the case of a child with DOCK8 deficiency and chronic, resistant HSV-1 mucocutaneous infections to illustrate clinical utility of viral whole genome sequencing to detect active and latent HSV resistance mutations

Methods
- Abstracted medical record data longitudinally
- Collected HSV-1 DNA from 7 stored viral culture specimens from 2015-2018
- HSV-1 DNA sequenced on an Illumina® MiSeq to >150X depth
  - Consensus genomes called using established HSV genome pipeline
  - Reads mapped to the HSV-1 strain reference genome (NC_001806)
- Sequence variants were checked against an online database of antiviral resistance mutations in:
  - UL23 (thymidine kinase)
  - UL30 (DNA polymerase)

Results: Resistance Assays
- Phenotypic testing:
  - Detected acyclovir resistance in HSV isolated from four samples while patient was on acyclovir
  - 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
  - Detected 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