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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)

Patient History

- 14 year-old boy with DOCK8, diagnosed at age 6
- Initial presentation:
  - Severe eczematous dermatitis
  - Eosinophilia, elevated IgE (initial 9660 kU/L)
  - Low CD4+ T cells (initial 248 cells/mm^3)
- Complications:
  - Chronic obstructive and interstitial lung disease
  - Recurrent infections:
    - *Staphylococcus aureus* skin infections
    - *Candida albicans* thrush
    - JC virus causing possible PML
    - HSV-1
- Prophylaxis: subcutaneous IgG, trimethoprim-sulfamethoxazole, acyclovir
- Mucocutaneous HSV-1 infections, biopsy confirmed HSV vegetans (Figures 1 and 2)
- Clinical response to acyclovir IV decreased over time
  - Advanced therapies to high-dose acyclovir IV, foscarnet IV, cidofovir IV, topical cidofovir cream, and/or interferon-alpha with variable clinical response

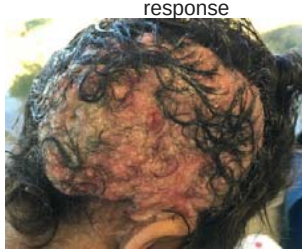

Figure 1

Figure 2

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

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