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### Genetic Predisposition to Neonatal Disseminated Herpes Simplex Virus Infection

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## **Genetic Predisposition to Neonatal Disseminated Herpes Simplex Virus Infection**

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**Background:** Neonatal disseminated herpes simplex virus (HSV) infection is a devastating disease with mortality rates as high as 80-90%, if left untreated. Despite advances in early diagnosis with risk-based screening, mortality rates have increased. Although case reports have identified genetic variants in Toll-like receptor 3 (TLR3) in patients with HSV encephalitis (HSE), whether variants in the TLR or similar pathways regulate susceptibility to disseminated disease remains unknown.

**Objective:** Our primary aim is to determine whether pathogenic variants in 7 genes associated with the TLR3 axis are present in infants with disseminated HSV. Our secondary aim is to discover whether variants in a broader range of genes linked to the immune response to viral infection are associated with any HSV phenotype.

**Design/Methods:** Hypothesis-generating study investigating the possibility of genetic predisposition for disseminated HSV. Blood samples, from infants diagnosed with HSV prior to 28 days of life, are collected for DNA extraction. Whole exome sequencing is performed using bar coded, high throughput sequencing (MiSeq, Illumina Inc.). Variants will be annotated by custom software (RUNES) based on predicted pathogenicity. Variants identified in our candidate genes (TLR3, UNC93B1, TICAM1, TRAF3, TBK1, and IRF3) and immunodeficiency genes will be annotated as per the American College of Medical Genetics and Genomics (ACMG) pathogenicity category (1-3). Variants with minor allele frequency (MAF) values < 1% will be included in the results.

**Results:** Seven infants with HSV have been genotyped: 5 disseminated and 2 Skin/Eye/Mouth (SEM) disease. There are 5 males and 2 females included, ranging from 30–40 weeks gestational age. Sequencing data from our primary analysis revealed that Infant 1 has 3 variants of interest (Table 1). Two variants were identified in the TBK1 gene (ACMG 1,2) and 1 variant in the IRF3 gene (ACMG 2). Variants in both genes have been associated with HSE. Our secondary analysis identified 7 potentially deleterious variants in genes associated with the immune response to virus infection, from viral recognition to induction of IFN production (Table 2).

**Conclusion:** Our preliminary data from the primary analysis suggests the TBK1 and IRF3 genes may play a role in the development of disseminated HSV, as well as HSE. Our secondary analysis suggests the presence of novel variants in genes associated with pathways related to the immune response to viruses. These may increase the susceptibility to disseminated neonatal HSV disease.