Supplementary Information

- **Supplementary Table 1.** Matching characteristics of the study cases and controls (N=159).
- **Supplementary Figure 1.** Principal Component Analysis plots for data distribution and quality control.
- **Supplementary Figure 2.** Differentially expressed proteins (post-hoc significant) for neonates with disseminated disease compared to controls.
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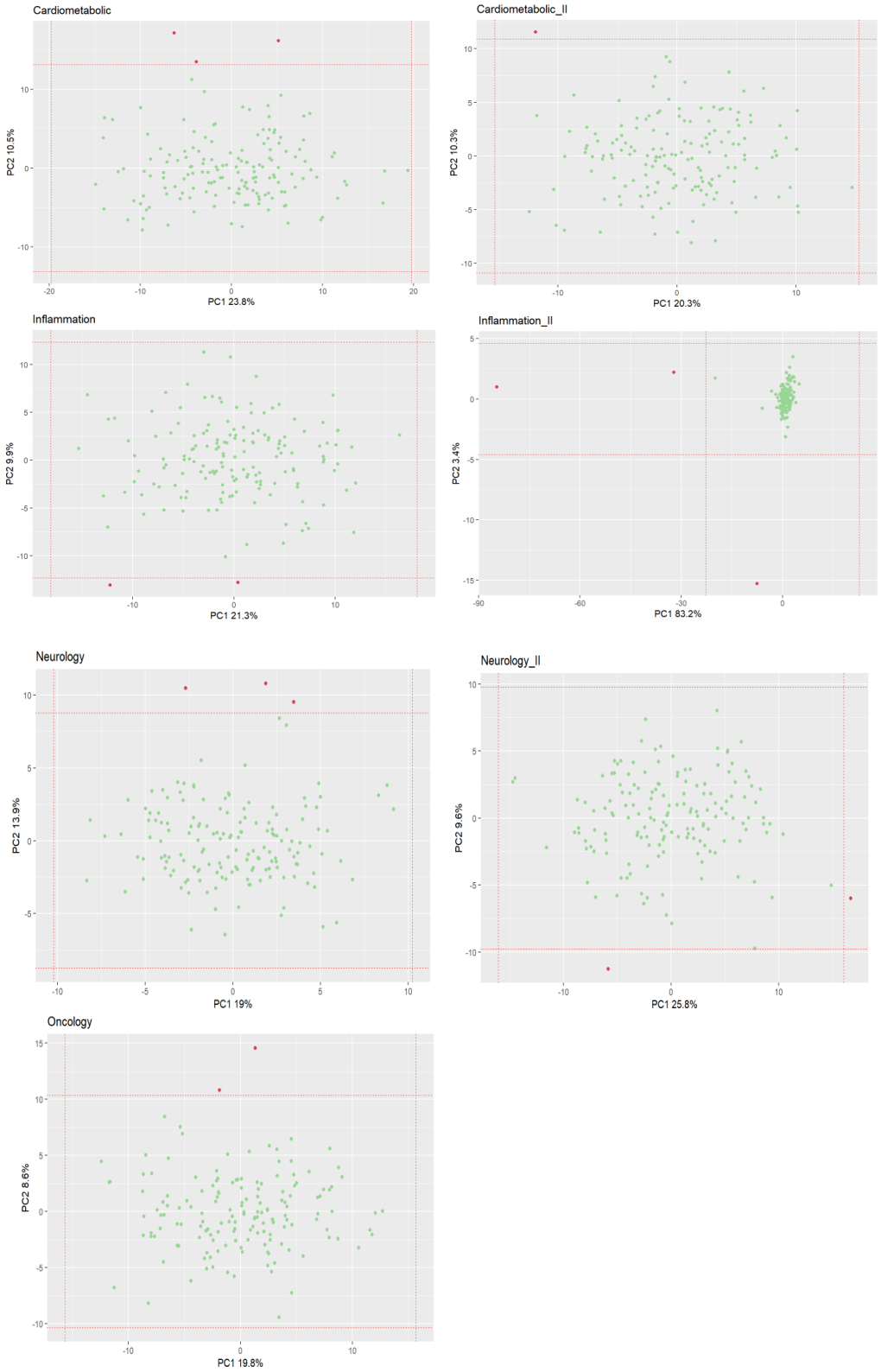
Supplementary Table 1. Matching characteristics of the study cases and controls (N=159).

	Cases* (n=53)	Controls* (n=106)
Age at DBS (days)	2 (2-4)	2 (2-4)
Gestational age (weeks)	39 (33-42)	39 (33-42)
Sex (male)	31 (58%)	61 (58%)
Birth weight (grams)	3,562 (1,975-4,560)	3,452 (1,848-4,920)

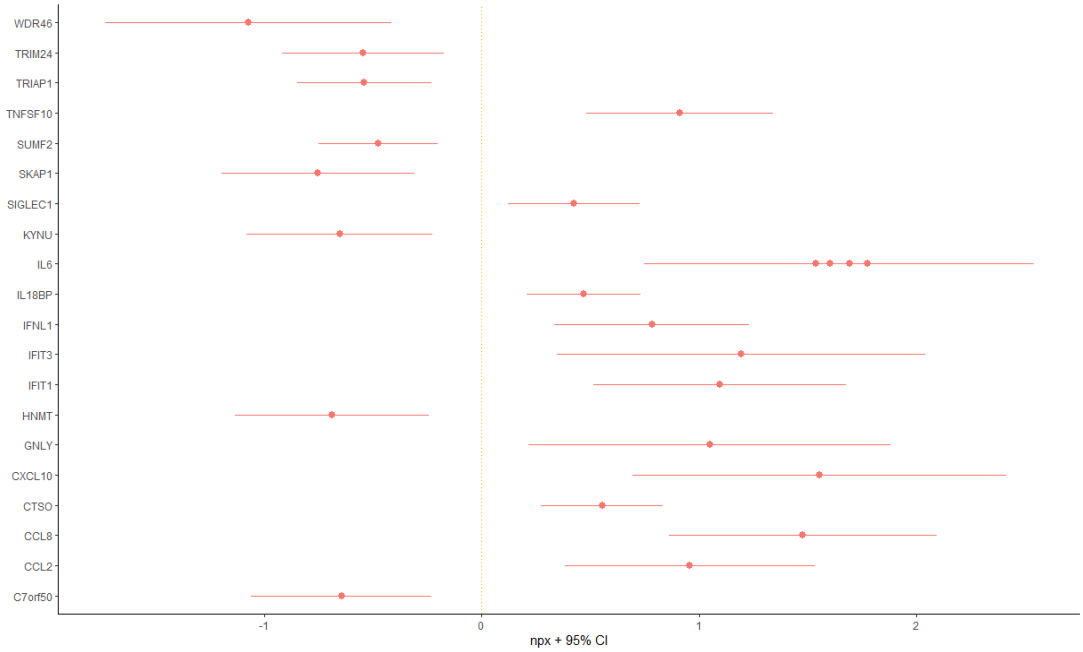
*Values presented are median (range) and n (%), DBS=dried blood spot

Supplementary Figure 1. Principal Component Analysis plots for data distribution and quality control.



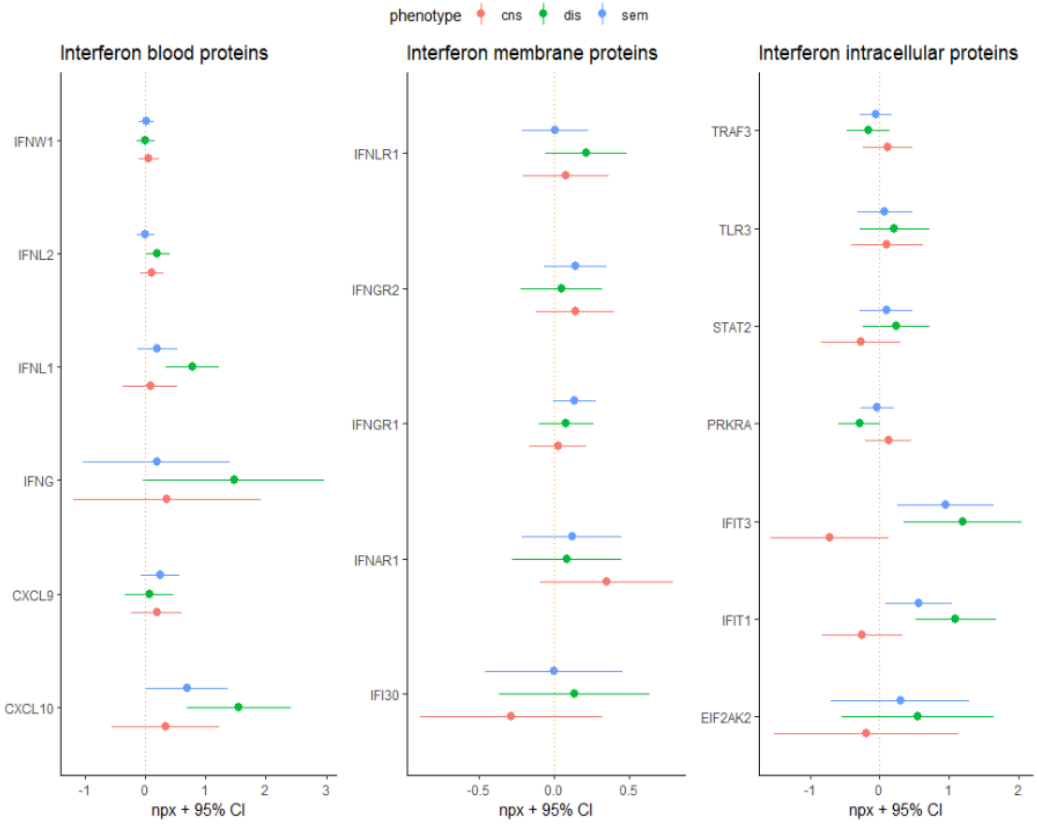
PCA plots depicting data quality control for each Olink Explore 3072 panel (Olink Proteomics Assays, Uppsala, Sweden). Red points represent outliers, defined as data points falling more than three standard deviations from either PC1 or PC2.

Supplementary Figure 2. Differentially expressed proteins (post-hoc significant) for neonates with disseminated disease compared to controls.



Forest plot of post-hoc significant proteins for neonates with disseminated disease compared to controls, depicting NPX mean differences with 95% confidence intervals.

Supplementary Figure 3. NPX levels of interferon response-associated proteins in the neonatal HSV phenotypes.



Forest plot of interferon response-associated proteins depicted with mean NPX differences + 96% confidence intervals according to neonatal HSV phenotype. DIS=disseminated, CNS=central nervous system, SEM=skin-eye-mouth.