DYING WITHOUT A DIAGNOSIS: USING GENOMIC SEQUENCING TO UNDERSTAND INFANT MORTALITY

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NEWBORN/GENOMIC MEDICINE

• How can we optimally apply our tools for genetic diagnosis in the neonatal intensive care unit (NICU)?
  • Infants who do not survive are likely to have genetic disorders
  • Infants with genetic disorders are more likely to not survive

CURRENT “UNDERSTANDING” OF THE LEADING CAUSE OF INFANT MORTALITY

• But what do these mortality statistics actually represent?
**GENETIC DISORDERS AND MORTALITY IN THE NICU**

- How many of our NICU deaths occur in the setting of a confirmed genetic diagnosis?
- Prior estimates range from 5-50% depending on definition of “genetic disorder”
  - The calculated prevalence of genetic disorders is directly related to our ability to identify them.

**UNDERSTANDING INFANT MORTALITY**

- The calculated prevalence of genetic disorders is directly related to our ability to identify and report them.

Exome sequencing was only used for a minority of infants (36) but resulted in a diagnosis for 14 (39%).
THE ROLE OF THE “MOLECULAR AUTOPSY”

- Postmortem evaluation, including exome or genome sequencing
- Goal to identify additional diagnoses
Established in 2008: One of the first Centers dedicated to rare disease research

- Gene Discovery Core
  - IRB-approved human research protocol and biobank
  - Enrollment includes:
    - Medical and family history and access to medical records
    - DNA sample from all participating family members
    - Fibroblasts, lymphoblastoid cell lines and tissue samples if available
    - Functional studies including cellular and animal (zebrafish/mouse) modeling options

IDENTIFYING DIAGNOSES IN INFANTS WHO HAVE DIED...

- Allows us to better understand infant mortality
  - Ultimately improve public health

- Better understand the presentations and molecular underpinnings of severe genetic diseases

- Provide valuable information to the family
UNDERSTANDING INFANT MORTALITY

- The calculated prevalence of genetic disorders is directly related to our ability to identify and report them.

THE PROBLEM WITH Q00-Q99...

- Historically, identified genetic conditions were mostly chromosomal.
  - Many/most had associated birth defects.
- In recent years, using ES for diagnosis has been high-yield.
  - 15/39, 38% in latter 2 years of infant mortality study.
  - (and rising).
- We identified near-equal proportions of chromosomal and monogenic disorders.
  - CHARGE syndrome, ARPKD.
  - Spinal Muscular Atrophy, Inborn errors of metabolism.

MANY INFANTS WITH LETHAL GENETIC DISORDERS DO NOT HAVE CONGENITAL ANOMALIES

- 333/573 congenital anomalies.
- 93/573 infants with a major congenital anomaly and a genetic diagnosis.
- 124/573 genetic disorders.
MANY DECEASED INFANTS WITH GENETIC DISORDERS ARE THEREFORE NOT REFLECTED AS SUCH IN CURRENT MORTALITY STATISTICS

Underlying cause of death coding for infants with or without genetic disorders

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FUTURE DIRECTIONS:

- Continuing to recruit, sequence, analyze undiagnosed infant deaths
- Improved understanding of infant mortality
  - Accurate counseling regarding the prognosis of rare genetic conditions
- Provide valuable information to families
  - Formal follow-up assessment after results disclosure to families
- Deep phenotyping is critically important

REFERENCES

- Hirata et al. ZC4H2 mutations are associated with arthrogryposis multiplex congenita and intellectual disability through impairment of central and peripheral synaptic plasticity. Am J Hum Genet 2013 2;92(5):681-95
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