Genomic Evaluation for Mitochondrial Disease in 1,935 Infants

Renkui Bai, MD, PhD, FACMG[1], Jane Juusola, PhD, FACMG[1], Gabriele Richard, MD, FACMG[1], Paul Kruszka, MD, FACMG[1]
[1]GeneDx LLC, Gaithersburg, MD

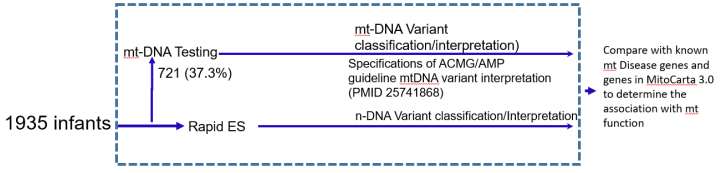
BACKGROUND

Mitochondrial disease is the largest class of inborn errors of metabolism and can affect multiple organ systems at different ages. In this study, we focus on mitochondrial disease phenotypes and genotypes in infants who have undergone rapid DNA sequencing. As more NICUs are utilizing this technology, it remains an open question if one should also include rapid mitochondrial DNA testing. This study evaluates the incidence of mitochondrial disease caused by both nuclear (n-DNA) and mitochondrial DNA (mt-DNA) in NICU patients.

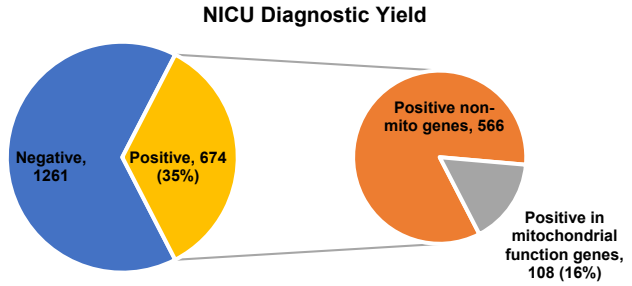
METHODS

This study is a retrospective review of 1,935 infants who received rapid exome sequencing, which included 721 (37%) infants who also received concurrent mt-DNA sequencing and deletion testing by whole mitochondrial genome amplification. n-DNA variants from rapid exome sequencing were classified according to ACMG/AMP guideline (PMID 25741868). Variants from mt-DNA were classified according to specifications of the ACMG/AMP guidelines for mt-DNA variant interpretation (PMID: 32906214). The positive results were compared with all the known mitochondrial disease genes as well as the genes in MitoCarta 3 to determine the association with mitochondrial diseases. Human Ontology Phenotypes (HPO) terms were extracted from the medical records of each infant and utilized for phenotype-driven genomic analysis

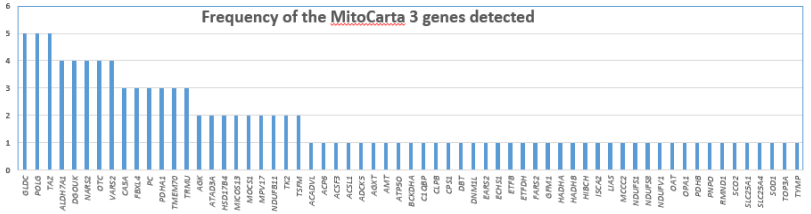
Rapid Exome Sequencing Plus mt-DNA test



RESULTS



The average age of the overall cohort was 2.2 months and the median age was 1.1 months. Male to female ratio was 1.2. The nuclear genes most frequently involved with mitochondrial dysfunction were *GLDC, POLG,* and *TAZ* (5/1,935). mt-DNA testing was done in 721 (37%) of infants, in addition to n-DNA testing. Eight infants (1.1%) had pathogenic mt-DNA variants with heteroplasmy levels that confirmed the diagnosis of mt-DNA diseases. The average age of these eight infants was 3 months and 75% were male. Two additional infants had a homoplasmic variant in MT-RNR1, m.1555 A>G, which conveys a risk for aminoglycoside induced deafness. Fourteen (1.9%) infants had pathogenic/likely pathogenic variants in mt-DNA and associated mitochondrial disease phenotypes, however the heteroplasmy levels were too low to confirm causality without testing additional tissues.



RESULTS

The most common phenotypes in positive n-DNA cases were hypotonia (40%), lactic acidosis (38%), seizures (36%), hypoglycemia (23%), and respiratory distress (25%). The most common phenotypes in diagnostic positive mt-DNA cases was lactic acidosis (88%), seizures (50%) and hypotonia (38%).

Positive rate of the 721 infants tested for Mito Genome

24 patients (3.33%) tested positive for pathogenic/likely pathogenic mtDNA variants:

8 patients with level of heteroplasmy sufficient to make a diagnosis

Disease	Variant	Gene	Heteroplasmy
Leigh syndrome	m.10158 T>C	MT-ND3	>95%
	m.10158 T>C	MT-ND3	Homoplasmic
	m.10191 T>C	MT-ND3	>90%
	m.8993 T>G	MT-ATP6	Homoplasmic
Pearson Syndrome	large mtDNA deletion (n=3)	Multiple	60-80%
Mutlisystemic mitochondrial disease	m.15635 T>C	MT-CYB	>95%

16 patients are non-diagnostic without additional test/information

13 Low-heteroplasmic Pathogenic/Likely Pathogenic variants including m,3243A>G (x2), m.12276 G>A, m.13513 G>A
1 LHON mutation
2 m.1555A>G associated with Aminoglycoside induced hearing loss

CONCLUSIONS

Mitochondrial disease is not an uncommon presentation in infants receiving rapid DNA sequencing. Although mt-DNA testing has a lower yield than n-DNA testing, it must be considered in NICU infants with symptoms associated with mitochondrial disease, especially hypotonia, lactic acidosis, seizures, hypoglycemia, and respiratory distress.