Development of a Targeted Second-Tier Genetic Test for Conditions Examined during Newborn Screening

Introduction

- Approximately four million children are born annually in the United States, most undergo state mandated newborn screening.
- In 2006 the American College of Medical Genetics and Genomics (ACMG) developed a recommended uniform screening panel (RUSP) to minimize variability between states.
- Most RUSP conditions are detected by tandem mass spectrometry.
- Through the use of genetic sequencing it is possible to detect the underlying genetic cause of RUSP conditions.
- Here we propose a step-wise approach to enhance traditional newborn screening and integrate genetic screening into population health using cost-effective, targeted sequencing to examine current RUSP conditions.

Core Condition Associated Gene(s) ACMG Code

- Methylmalonic aciduria MTM2, CBL, MTTP, MTH REV
- Homocystinuria MTHFR II
- Medium-chain Acyl-CoA Dehydrogenase Deficiency AGG6M MCKD
- Very Long-chain Acyl-CoA Dehydrogenase Deficiency ACADM VKD
- T3, T4, TSH Deficiency ACAT1, AHCY, MAT1A
- Argininosuccinic Acidemia ASS ASA
- Cofactor Deficiency ASS ASA
- Tryptophan, Tyrosine Deficiency ASS ASA
- Glutamine Storage Disease Type II GAA GIDE
- T2, T3, T4, TSH Deficiency NR3C1, NR3C2 MCTD
- Succinyl CoA Deficiency ACS
- 3-Methylcrotonyl-CoA Carboxylase Deficiency AK2, AK3 MCKD
- Methylmalonic Acidemia (Cobalamin disorders) AKM2, ARMD CBL, CBS
- Methylenetetrahydrofolate Dehydrogenase Deficiency BHMT BHMT
- Histidine Uptake Defect/Carnitine Transport Defect HUAT CH
- Primary Congenital Hypothyroidism NIS, TTR, TPO, TH1A, TH1B, TH2A, TH2B, THY1

Secondary Condition Associated Gene(s) ACMG Code

- Short-chain Acyl-CoA Dehydrogenase Deficiency ACSAD1 SDAD1
- 2-Methylbutyryl-CoA Dehydrogenase ACM5 ZMBD
- Hyperargininemia ARSD ARS
- Tryptophan Cofactor Deficiency TPMT TPMT
- Carnitine palmitoyltransferase type I deficiency CPT1A CPT1A
- Carnitine palmitoyltransferase type II deficiency CPT2 CPT2
- Glutaric acidemia type I EAAT EAAT
- Glutaric acidemia type II EAAT EAAT
- Glutaric acidemia type III ETAH ETAH
- Glutamine synthetase deficiency GLN1 GLN1
- Glycine Dehydrogenase Deficiency GLDH GLDH
- Biotinidase defect in cofactor biosynthesis BPI BPI
- Hypophosphatasia TNS1 TNS1
- Medium/short-chain 1-Hydroxy-CoA Dehydrogenase Deficiency HCDH HCDH
- Tyrosinemia, type III ARAS ARAS
- 2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase PHGDH PHGDH
- Melodea acidemia MELD MELD
- Methylmalonic acidemia with homocystinuria MMACHC, MMACHD CBS, CBS
- 2-Hydroxyglutarate Dehydrogenase ALKBH5 ALKBH5
- 3-Methylglutaconic aciduria GCD3 GCD3
- Biotinidase Defect in Cofactor Biosynthesis BIDI BIDI
- Biotinidase Defect in Cofactor Biosynthesis BIDI BIDI
- Citrullinemia, type II SLC19A3 SLC19A3
- Carnitine amidotransferase II deficiency CATT CATT
- Tricaprinase deficiency TBCD TBCD
- 3-Methyl-CoA Dehydrogenase TMC cd, TMC3 TMC

Table 1. Primary and secondary ACMG RUSP conditions and associated genes.

Methods

- We used molecular inversion probes (HEAT-Seq, Roche-NimbleGen) to examine 72 genes associated with RUSP primary and secondary conditions as a possible second-tier genetic screen.
- We performed HEAT-Seq library preparation on eight samples that had previously undergone whole-exome sequencing (WES) (SureSelectXT, Agilent) and compared the exon coverage, base-level coverage and variant detection between the two methods.

Acknowledgments & Sources

We would like to acknowledge funding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and The National Human Genome Research Institute (NHGRI) for RFA-HD-13-101.

Conclusions & Future Implications

We anticipate that this approach could be translated as an economical secondary genetic screen for current newborn screening, and serve as a proof of concept for adding other medically actionable conditions to the current recommended list for newborn screening.