Newborn Screening for Pompe Disease in New York

Joseph Orsini, Ph.D.
February 29, 2016
Methodology

1. MS/MS using CDC provided ASRs (Oct. ‘14- May ‘15)

2. MS/MS using Perkin Elmer ASRs with universal buffer
Cutoffs and Testing Algorithm

All specimens tested for Enzyme activity

- < 20% of daily mean
- > 20% of daily mean

* Retested in duplicate (or more)

Average of 3 samples ≤ 15%

DNA testing GAA

1 or more mutations

Screen Positive Referral

Average of 3 samples > 15%

No mutations

Screen negative

*Plan to perform retest with 6-Plex (FP)
Screening Results

1. Infants screened: 330,000
2. 89 Infants with ≤ 15% (DNA tested)
3. 11 Infants with pseudo only (not referred, ~12-15%)
4. 18 Infants with other non-disease causing variants (not referred, 12-15%)
5. 60 infants referred (≥ 1 mut, 0.018% screen positive rate)
Follow-up results (60 referrals)

1. Infantile Pompe disease = 1 (<8%)
2. Infants with two “mutations”/low diagnostic enzyme = 28
   a. 11 with known pathogenic mutations (“probable cases”)
   b. 10 with 1 known pathogenic/1 VOUS (“possible cases”)
   c. 6 with two VOUS (activity above LOPD range at diagnostic lab)
   d. 1 referral - awaiting Dx lab results
3. Carriers: 31 (activities generally >12%, often premature infants – tend to have lower activity, dx lab activities in carrier range)
4. Current case classifications are internal, subject to change

*For more information on genotypes and diagnostic testing results see Poster: “The LC-MS/MS Assay of Leukocyte Acid α-Glucosidase Activity Reliably Differentiates Early-onset and Late-onset Pompe Disease.” Chunli Yu, et al.
Dried blood spot analysis: attenuated activity modes

100%

- Low hematocrit
- Low leukocytes
- Enzyme reducing SNP
- Pseudo-def
- Mutations/VOUS

Activity attenuating effects
Expected the unexpected

1. Only 1 infant in 330,000 detected with infantile Pompe disease. Lower than expected (reported incidence all forms 1/40,000).
2. 21 infants (1/15,714) with “potential” for LOPD. Higher than expected
3. Many cases with pseudo-deficiency alleles as background and other variants detected
4. Prediction of if/when infant will become symptomatic very difficult
5. Families responses vary (cultural, socio-economic, physician experience/knowledge)
Conclusions and improvement opportunities

1. Population dependence on screening results
2. Use of hard cutoffs in “single” enzyme analysis leads to higher positive rates – Exploring use of Region IV CLIR software*
3. Dx MS/MS leukocyte assay: more LOPD cases needed to better define
4. Need for improved genotype/phenotype correlations
5. Short-term follow-up is “long-term” follow-up when screening diseases with common late onset phenotypes

*CLIR: Collaborative Laboratory Integrated Reports.

No “cutoffs” uses ratios with other LSDs/markers
Acknowledgements

Monica Martin, Chad Biski, Ryan Wilson (screening lab staff)
Michele Caggana (NBS Program Director)
Colleen Stevens, Erin Hughes (DNA testing, interpretations)
Chunli Yu, Melissa Wasserstein (diagnostic testing)
Priya Kishnani, Deeksha Bali: case review
Patrick Hopkins, Carlene Campbell, Tracy Klug (technical support, positive controls)
Hui Zhou, Bob Vogt (quality control specimens, distribution of reagents)
NIH-NICHHD (funding)
Thank You!!