SCID Secondary Targets Identified by the Texas Newborn Screening Program

D. Freedenberg, R. Lee, D. Johnson, G. Scott, K. LaBoard and K. Hess, Texas Department of State Health Services, Austin, TX

Abstract

The Texas Newborn screening Program initiated screening for SCID in December of 2012. The methodology utilized is detection of TREC’s as previously reported. As a two screen state, the TREC screening results are reported on both screens. Since initiation of screening we have detected 14 babies with SCID, and over 250 babies with a secondary condition predisposing to low TREC values. The majority of out of range screens reflect babies with significant health issues. Although low birth rate cutoffs are utilized, a large proportion of these children have prematurity with and without significant complications. The largest proportion of children with low TRECs and a secondary condition have congenital heart disease. The Newborn Screening program has chosen to categorize the secondary conditions in broad categories recognizing that several conditions can be classified in more than one category. DiGeorge syndrome, congenital heart disease, chromosomal abnormalities, multiple congenital anomalies, lymphatic/fluid imbalances, prematurity, are among the more common underlying diagnosis in these children. Discussion of the differences in underlying diagnosis in children with out of range first screens, and out of range subsequent screens will be addressed. As a two screen state many of the children have undergone heart surgery by the time of collection of the second screen accounting for the large proportion of low TREC values. The Texas Newborn Screening program will present our screening results for secondary targets identified by SCID newborn screening.

Presenter: Debra Freedenberg, MD, PhD, Texas Department of State Health Services, Newborn Screening and Genetics Unit, Austin, TX, Phone: 512.776.3101, Email: debra.freedenberg@dshs.state.tx.us

Summary

Severe Combined Immunodeficiency (SCID) is a group of rare inherited immune disorders in which T lymphocytes fail to develop and B lymphocytes are either absent or compromised. The reported incidence is ~1/58,000 with over 15 known gene defects; the most common of which is an X linked form. Untreated babies develop recurrent bacterial, viral, and fungal infections. Early treatment by hematopoietic stem cell transplant (HSCT) can be lifesaving.
The Texas Newborn Screening Program implemented statewide screening for SCID on 12/1/2012. Texas requires two newborn screens with SCID screening on both screens. Approximately 731,312* births occurred during the first 22 months of screening. Testing utilized a real time polymerase chain reaction method. A statewide ad hoc pediatric immunologist work group was engaged to assist with designing the laboratory algorithm and follow up protocols prior to implementation.

Our screening algorithm utilized T-cell Receptor Excision Circles (TREC) as the primary marker and RNase P as a control gene. Samples that had an RNase P Ct of >28.5 and <150 TREC copies per L were considered unsatisfactory. Samples that had less than 200 copies of TREC /L were retested in duplicate from the same specimen. If the repeat testing noted >150 copies of TREC/L, the sample was considered normal. If there were less than 110 copies/L, the sample was considered abnormal. For babies that weighed less than two kg, TREC quantities between 110-150 copies/L were considered borderline. For babies greater than two kg, TREC copies between 110-150 copies/L were considered abnormal. Follow up actions included referral of all babies who had undetectable TREC levels as noted in the chart below.

<table>
<thead>
<tr>
<th>Result of 1st Screen</th>
<th>Result of 2nd Screen</th>
<th>Result of 3rd Screen</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Undetectable</td>
<td>All (Abnormal Low or Borderline or Unsat or Normal)</td>
<td></td>
<td>Referral</td>
</tr>
<tr>
<td>Abnormal Low</td>
<td>Abnormal Low</td>
<td></td>
<td>Referral</td>
</tr>
<tr>
<td>Abnormal Low</td>
<td>Unsat</td>
<td></td>
<td>Repeat</td>
</tr>
<tr>
<td>All</td>
<td>Undetectable</td>
<td></td>
<td>Referral</td>
</tr>
<tr>
<td>Abnormal Low or Borderline or Unsat</td>
<td>Normal</td>
<td></td>
<td>No further follow up - Cleared</td>
</tr>
<tr>
<td>Normal</td>
<td>Abnormal Low or unsat</td>
<td></td>
<td>Repeat</td>
</tr>
<tr>
<td>Normal</td>
<td>Borderline</td>
<td>Unsat</td>
<td>Repeat</td>
</tr>
<tr>
<td>Normal</td>
<td>Abnormal Low</td>
<td>Unsat</td>
<td>Repeat</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Abnormal Low</td>
<td>Repeat if normal BW. Repeat at 37 wks CGA if LBW.</td>
</tr>
<tr>
<td>Normal, Unsat, Borderline, Abnormal Low</td>
<td>&lt; 2 kg</td>
<td>@37 weeks CGA Abnormal low, borderline, Undetectable</td>
<td>Referral</td>
</tr>
<tr>
<td>&gt; 2 kg Unsat</td>
<td>&gt; 2 kg Unsat or Undetectable</td>
<td></td>
<td>Referral</td>
</tr>
</tbody>
</table>

301 (0.04%) babies were referred for clinical evaluations and were identified with medical conditions. We utilized the NBSTRN R4S categorization. Diagnostic category was based on information/lab results received from a clinician. The categories of secondary conditions were: Syndromes with T cell impairment, Secondary T cell lymphopenia or T cell impairment other than preterm alone, and preterm infants with no other recognizable disorder. 64% of the babies who met criteria for referral had T cell lymphopenia other than preterm alone. These children had a spectrum of congenital anomalies including congenital heart disease. 13% of the babies had a DiGeorge Spectrum disorder. We also detected 15 children with SCID during this period.
All children with confirmed SCID had an abnormal first screen. 22% of the children with DiGeorge spectrum had abnormal TREC values on the second screen only. 84% of children with congenital heart disease and an abnormal TREC value had an abnormal second screen only.

Lessons learned included that the start-up period had more presumptive positives than anticipated and protocols required re-evaluation and adjustment. Most non-SCID children who met criteria for referral to an immunologist had significant health issues with a variety of congenital anomalies. Few preterm babies who had abnormal TREC copies /i in their first two screens required immune evaluation when rescreened at 37 weeks corrected gestational age (pre-term babies with undetectable TRECs were referred). It is very difficult to categorize secondary conditions detected by SCID newborn screening. For instance DiGeorge syndrome could be classified as chromosomal, multiple congenital anomalies, or congenital heart disease.

*preliminary data

**Homozygosity for a Carnitine Palmitoyltransferase 1A Genetic Variant is Associated with an Increased Risk for Infant Mortality: Implications for Newborn Screening**

D. Koeller, Oregon Health & Science University, Portland, OR

**Abstract**

**Background:** MS/MS based newborn screening in Alaska revealed a high prevalence of a carnitine palmitoyltransferase 1A (CPT1A) sequence variant (c.1436C→T, p.P479L) associated with reduced catalytic activity in Alaska Native infants. In Western and Northern Alaska the variant allele (Arctic...
Variant) is the wild type (most common) allele in Alaska Native infants (gene frequency = 0.7). In the same region of Alaska infant mortality is almost twice as high (11.4/1,000 vs. ~6/1,000) as in Anchorage and the rest of the state.

**Methods:** Based on the association of CPT1A deficiency and other fatty acid oxidation disorders with infant death we performed an unmatched case-control study to test the hypothesis that homozygosity for the arctic variant is a risk factor for infant death. Cases were 110 Alaska Native infant deaths; controls were 395 Alaska Native births from the same time period. We conducted two analyses: one limited to infants from the regions of highest prevalence, and one limited to homozygous or heterozygous infants. Genotyping was done via allelic exclusion assay.

**Results and Discussion:** The odds ratio (OR) of homozygosity for the arctic variant in normal birth weight infants that died in regions of high prevalence was 3.0 (95% CI: 1.4-6.3). Infants homozygous for the variant were also significantly more likely to have died of infectious disease related causes (OR = 2.9; 95% CI, 1.0, 8.0), and to have had a prior history of pneumonia (OR = 15; 95% CI, 1.9, 125). The increased risk of infant mortality associated with homozygosity for the arctic variant of CPT1A may account for the majority of the increased risk in Western and Northern Alaska. This may be mediated in part by an increase in infectious disease risk. The MS/MS based screening algorithm currently used in Alaska has a low ascertainment of infants homozygous for the variant (~10%). The association of negative health outcomes with the variant has prompted Alaska public health and Alaska Native health leadership to call for full ascertainment by newborn screening. Using the post-analytical interpretive tools of the Region 4 Stork (R4S) collaborative project a new screening algorithm was created that combines MS/MS and DNA testing, with a predicted sensitivity of >90% and specificity >99%

**Preliminary results of newborn screening with this algorithm will be discussed.**

**Presenter:** David Koeller, MD, Oregon Health & Science University, Molecular & Medical Genetics, Portland, OR, Phone: 503.494.7703, Email: koellerd@ohsu.edu

**Summary**

The Alaska Newborn Metabolic Screening Program started using tandem mass spectrometry (MS/MS) for newborn screening in October 2003. The screening panel included all of the core conditions and secondary targets recommended by the American College of Medical Genetics, including carnitine palmitoyltransferase 1A (CPT1A) deficiency, a rare autosomal recessive disorder of fatty acid oxidation that impairs fasting ketogenesis and gluconeogenesis by the liver. Symptoms include lethargy and hypoketotic hypoglycemia, which are triggered by fasting and exacerbated by stress, such as fever and infection. As with other fatty acid oxidation disorders there is also an increased risk of unexplained infant death. Symptoms can be prevented by early identification and intervention, underscoring the importance of newborn screening.

During the first 5 years of MS/MS based screening in Alaska (January 2004 through December 2008), an unexpectedly high number of infants (n = 176; birth prevalence, 0.33%) had a positive newborn screen for CPT1A deficiency (elevation of the C0/C16+C18 ratio). All of the infants were Alaska Natives, and were homozygous for a single sequence variant (c.1436C→T, p.P479L) that was previously identified in Inuit populations of Canada and Greenland, and results in a partial loss (80%) of catalytic activity (1, 2). We have named this sequence variant The Arctic Variant of CPT1A, based on its high prevalence in the sub-arctic regions of Alaska, Canada, and Greenland.
In spite of the large number of infants being identified with evidence of reduced CPT1A activity, there was concern that many were not being found by newborn screening. Therefore we undertook a quality assessment in which newborn blood spots collected from infants born over a 3-month period (n=2,409) were evaluated by both MS/MS and DNA sequence analysis. We found that using an elevation of the C0/C16+C18 ratio (>100) to identify infants homozygous for the CPT1A arctic variant was ascertaining fewer than 10% of those identified by DNA analysis (Table 1).

<table>
<thead>
<tr>
<th>Ratio</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>130</td>
<td>0% (0/166)</td>
<td>100% (2243/2243)</td>
<td>Undefined</td>
<td>93.1% (2243/2409)</td>
</tr>
<tr>
<td>100</td>
<td>3.0% (5/166)</td>
<td>100% (2243/2243)</td>
<td>100% (5/5)</td>
<td>93.3% (2243/2404)</td>
</tr>
<tr>
<td>40</td>
<td>61.4% (102/166)</td>
<td>99.9% (2240/2243)</td>
<td>97.1% (102/105)</td>
<td>97.2% (2240/2304)</td>
</tr>
<tr>
<td>20</td>
<td>99.4% (165/166)</td>
<td>95.1% (2132/2243)</td>
<td>59.8% (165/278)</td>
<td>100% (2132/2133)</td>
</tr>
</tbody>
</table>

This analysis also showed that among the 633 Alaska Native infants born during the 3-month period of the assessment, 165 (26.1%) were homozygous and 218 (34.4%) were heterozygous for the arctic variant. The prevalence was highest in Alaska’s northern and western regions, where the arctic variant is the most common (wild type) form of the gene (allele frequency, 0.7), and was found to be in Hardy-Weinberg equilibrium (1).

The infant mortality rate in the regions of Alaska where the CPT1A arctic variant is most prevalent is almost twice as high (11.4/1,000 vs. ~ 6/1,000) as in Anchorage and the rest of the state. Based on the association of CPT1A deficiency and other fatty acid oxidation disorders with infant death we performed an unmatched case-control study to test the hypothesis that homozygosity for the arctic variant of CPT1A is a risk factor for infant death. Cases consisted of 110 Alaska Native infant deaths; controls were 395 Alaska Native births from the same time period.

To account for potential effects of geographic variability on known risk factors for infant mortality and the prevalence of the arctic variant, we performed three separate analyses. The first included all study subjects from all regions of Alaska. The second was limited to study subjects residing in Western and Northern Alaska, where the prevalence of the variant is greatest. The third analysis included study subjects from all regions of Alaska, but was limited to those that were either homozygous or heterozygous for the variant allele. For each analysis, we created logistic regression models that included mortality as the independent variable, and CPT1A genotype as the primary dependent variable of interest. Adjustments were made for three potentially confounding variables that we previously identified to be associated with risk of infant mortality; maternal prenatal alcohol or tobacco use, maternal education, and a composite variable reflecting the involvement of a father figure. We also conducted a separate set of analyses limited to normal birth weight infants (2500 grams or greater).

Homozygosity for the arctic variant was associated with infant mortality in all analyses (Table 2). The association was strongest (adjusted odds ratio [OR] = 2.5; 95% confidence interval (CI) 1.3, 5.0) among residents of Western and Northern Alaska. Exclusion of low birth weight infants strengthened the association within this sub group (OR = 3.0; 95% CI, 1.4, 6.3), but had little effect when the analysis included all subjects, or was limited to only those either homozygous or heterozygous for the variant (manuscript in preparation).
Table 2. Association between Homozygosity for the Arctic Variant of CPT1A and Infant Mortality

<table>
<thead>
<tr>
<th>Analytic Subgroup</th>
<th>Rate of Homozygosity for the Arctic Variant</th>
<th>Odds ratio (95% CI)</th>
<th>Adjusted* odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
<td></td>
</tr>
<tr>
<td>All birth weights</td>
<td>46 of 110 (42%)</td>
<td>119 of 395 (30%)</td>
<td>1.7 (1.1, 2.6)</td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygous and heterozygous variant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residents of Western and Northern Alaska</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46 of 79 (58%)</td>
<td>119 of 269 (44%)</td>
<td>1.8 (1.1, 2.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>38 of 58 (66%)</td>
<td>1.8 (0.98, 3.3)</td>
</tr>
<tr>
<td>Birth weight ≥ 2,500 g.</td>
<td>39 of 94 (41%)</td>
<td>112 of 377 (30%)</td>
<td>1.7 (1.1, 2.7)</td>
</tr>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homozygous and heterozygous variant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residents of Western and Northern Alaska</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39 of 69 (57%)</td>
<td>112 of 258 (43%)</td>
<td>1.7 (0.99, 2.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33 of 48 (69%)</td>
<td>2.2 (1.1, 4.2)</td>
</tr>
</tbody>
</table>

*Adjusted for maternal education, maternal prenatal alcohol and tobacco use, and a composite variable combining marital status and presence of the father’s name on the birth certificate.

We also observed a statistically significant association between homozygosity for the CPT1A arctic variant and death associated with infectious diseases (OR = 2.9; 95% CI, 1.0, 8.0), and found that children with a pre-morbid history of a severe infectious disease (pneumonia, sepsis, meningitis), or prior hospitalization for any cause, were more likely to be homozygous for the arctic variant than children who did not have an earlier infectious disease episode.

These results indicate that risk of infant death associated with homozygosity for the arctic variant of CPT1A likely accounts for a significant amount of the increased rate of infant mortality observed in Western and Northern Alaska. We also confirmed our prior observation that homozygosity for the arctic variant is associated with increased rates of infectious diseases (3), which likely contributes to the increased rate of infant mortality due to the reduced fasting tolerance in homozygous infants (4).

The association of negative health outcomes with the variant has prompted Alaska public health and Alaska Native health leadership to call for changes in the approach to newborn screening to overcome the current low rate of ascertainment of infants homozygous for the arctic variant (~10%). Using the post-analytical interpretive tools of the Region 4 Stork collaborative project we generated a new algorithm that incorporates additional MS/MS analytes (C2, C3, C18:1) and ratios (C16+C18:1/C2, C3/C16), in combination with reflex DNA analysis, resulting in a predicted sensitivity of 90% with greater than 97% specificity. However, based on the prevalence of the CPT1A arctic variant, a test with only 90% sensitivity will mean that ~70 infants per year are not identified. A plan to begin DNA testing for the CPT1A arctic variant on all newborn screening samples from Alaska infants, which we believe is the only way to achieve full ascertainment and maintain adequate specificity, is now being considered. Plans for a comprehensive long term follow up study of the infants that will be identified by universal DNA testing are also being developed, in order to further evaluate the clinical effects of the CPT1A arctic variant. Of the many unanswered questions still to be addressed, perhaps the most intriguing is the nature of the beneficial effects of the arctic variant that have resulted in its apparent positive selection and high prevalence in sub-arctic indigenous populations.

References


VLCADD Pacific Island Mutation? A Study of Hawaii Newborn Screening Dried Blood Spots

K. McWalter¹, C.A. Valencia², K. Zhang², N. Barasa², D. Kissel², A. Strauss², D. Sesser³, S. Mann¹;
¹Hawaii Department of Health, Honolulu, HI, ²Cincinnati Children’s Hospital Medical Center, Cincinnati, OH, ³Oregon State Public Health Laboratory, Hillsboro, OR

Abstract

Very Long Chain Acyl-Coenzyme A Dehydrogenase deficiency (VLCADD) reportedly occurs in 1/30,000 people. It can be associated with mild to severe phenotypes. Clinical signs and symptoms may include cardiomyopathy, pericardial effusion, arrhythmias, hypotonia, hepatomegaly, hypoglycemia, muscle cramps, and pain. VLCADD has a strong genotype-to-phenotype correlation. 99.8% of Hawaii’s (HI) infants receive NBS. Bloodspots are retained for 12 months for quality improvement (QI) purposes. In HI, 44 children have screened positive for VLCADD since 2007. Of those, 19 had at least one 1226C>T mutation (11 homozygotes, four heterozygotes, and four compound heterozygotes). All 19 children are of Hawaiian/Pacific Islander/Asian ethnicity. The number of HI 1226C>T homozygotes identified (11/≈133,000 births from 2007-2013) is roughly 2.5 times the nation-wide incidence rate of all VLCADD homozygotes (1/30,000). The 1226C>T mutation has been reported as pathologic. However, few of the HI cases have clinical signs or symptoms. This project aimed to clarify the incidence of the 1226C>T VLCADD mutation in HI and was approved as a QI effort by the HI Dept of Health IRB. Results will aid the NBS program and clinicians provide better follow-up and genetic counseling for children who screen positive. One-thousand HI NBS bloodspots from January (600) and February (400) 2014 were sampled from Asian/Pacific Island infants. DNA was extracted from peripheral blood collected on NBS bloodspot forms according to standard protocols. Mutation analysis is underway at the Cincinnati Children’s Hospital Medical Center Molecular Genetics Lab: genotyping by real-time polymerase chain reaction on an ABI Prism 7700 Sequence Detection System (Applied Biosystems, Carlsbad, CA, USA), using a TaqMan single nucleotide polymorphism (SNP) genotyping assay for the ACADVL c.1226C>T (p.409M) mutation (Applied Biosystems). Statistical analysis will be done using SPSS, including frequencies and significance. Project results will (1) help the HI NBS Program correctly identify and interpret VLCADD results; (2) aid HI’s clinical genetics professionals in their discussions with parents of newborns with the 1226C>T mutation; and (3) add to the current knowledge of the 1226C>T mutation and its classification as a pathogenic mutation.

**Summary**

**Background:** Very Long Chain Acyl-Coenzyme A Dehydrogenase deficiency (VLCADD), a condition identified by newborn screening (NBS), reportedly occurs in 1/30,000 people. It can be associated with phenotypes ranging from relatively mild to severe. Clinical signs and symptoms may include hypertrophic or dilated cardiomyopathy, pericardial effusion, arrhythmias, hypotonia, hepatomegaly, intermittent hypoglycemia, muscle cramps, muscle pain, and exercise intolerance.

VLCADD is caused by mutations in the *ACADVL* gene. *ACADVL* mutations have shown strong genotype to disease phenotype correlation. In general, two null mutations tend to correlate with more severe, childhood-onset disease, while two alleles that result in some residual enzyme activity tend to correlate with less severe disease (OMIM). The 1226C>T mutation (p.Thr409Met) is classified as a pathogenic variant and has been observed more commonly among individuals of Pacific Island ancestry than in other populations (GeneReviews).

In Hawaii (HI), the metabolic newborn screening (NBS) rate is inclusive: 99.8% of HI’s infants receive NBS. The dried bloodspots are retained by HI’s contracted NBS laboratory, the Oregon State Public Health Laboratory, for 12 months for quality improvement (QI) purposes. Between 2007 and 2013, the HI NBS Program had 44 children screen positive for VLCADD. Of those cases, 19 had at least one copy of the 1226C>T mutation (11 homozygotes, four heterozygotes, and four compound heterozygotes). All 19 cases were infants of Hawaiian/Pacific Islander/Asian ethnicity. While the 1226C>T mutation is classified as a pathogenic variant, almost none of the children identified in HI via a positive NBS have had clinical signs or symptoms.

The number of 1226C>T homozygotes identified in HI (11/~133,000 births in the years 2007-2013) is roughly 2.5 times the nation-wide incidence rate of all VLCADD homozygotes combined (i.e., including all mutations) of 1/30,000. The frequency of the T allele in HI between 2007-2013, based on positive NBS results, was 0.011%. For QI purposes, this project’s aim was to clarify the incidence of the 1226C>T VLCADD variant (T allele frequency) in HI to help improve genetic counseling for families.

**Methods:** This project was approved as a QI effort by the HI Department of Health Institutional Review Board. One-thousand HI NBS dried bloodspots collected in January (600) and February (400) 2014 were randomly sampled from newborns of Asian and/or Pacific Islander ancestry. De-identified samples were shipped from the Oregon laboratory via FedEx to Cincinnati. Mutation analysis of the NBS bloodspot samples was conducted at the Cincinnati Children’s Hospital Medical Center Molecular Genetics Laboratory. DNA was extracted from the dried NBS bloodspots according to standard protocols. Technical issues precluded the use of a SNP assay for genotyping; homozygotes were indistinguishable from heterozygotes. So, DNA samples were genotyped by targeted Sanger sequencing for the *ACADVL* c.1226C>T (p.409M) mutation. Some tests failed due to poor DNA quality, even after repeated attempts. Descriptive statistics were generated, including the number of 1226C>T heterozygotes and homozygotes, genotype frequencies, and allele frequencies.
Results: In total, 998 NBS bloodspots were sent from the Oregon State Public Health Laboratory to the Cincinnati Children’s Hospital Medical Center Molecular Genetics Laboratory for testing. Sanger sequencing was completed on 850 samples; the remaining 148 samples provided DNA yields that were too low for testing to be completed, despite multiple attempts. Sanger sequencing was used to genotype the wildtype alleles (C) and variant alleles (T) of ACADVL. Results showed that 807 infants (94.9%) were homozygous wildtype (CC) at this locus, while 43 infants (5.1%) were CT heterozygotes, and zero infants (0%) were TT homozygotes. In this sample, the C allele frequency was 97.5% and the T allele frequency was 2.5%.

Discussion: While the allele frequency of the T allele in our sample population was anticipated to be elevated, based on observations of this variant being more common in people of Pacific Island ethnicity, results showed that it was significantly higher (2.5%) than expected, given our past NBS results. Between 2007 and 2013, eleven 1226C>T homozygotes, four heterozygotes, and four compound heterozygotes were identified via HI NBS (~133,000 births occurred over that time period). This is a total of 30 T alleles, resulting in an allele frequency of 0.011%. The current study, however, identified an allele frequency that is several hundred times higher than the allele frequency detected by HI NBS. Granted, this study consisted only of samples from infants of Asian and/or Pacific Islander background, potentially concentrating the allele frequency. However, the Asian and Pacific Island population in HI together comprises roughly 48% (this only includes individuals of one ethnic background; i.e., does not include individuals of two or more ethnicities, which makes up more than 23% of HI’s population and undoubtedly includes a individuals of part Asian and/or part Pacific Island ethnicity) (United States Census Bureau, 2013). Therefore, a conservative estimate would identify at least half of HI’s population as having Asian and/or Pacific Island background. This indicates that the T allele frequency identified in the current study is still elevated over what would be expected, given NBS results between 2007 and 2013. Those NBS results showed that HI had an incidence rate 2.5 times the nation-wide incidence rate of all VLCADD homozygotes (i.e., including all mutations) of 1/30,000. The current study shows that the HI T allele frequency is also elevated.

The increased rate of individuals either homozygous for VLCADD or possessing at least one T allele may be explained by a founder effect within the Asian and/or Pacific Island groups. What is also very interesting is personal communication with clinical geneticists who work with Asian and/or Pacific Islander populations and who report no signs or symptoms of disease in individuals homozygous for the 1226C>T variant. This, plus the increased allele frequency in HI, brings into question the current classification of this variant as “pathogenic”.

Results of this QI project will (1) facilitate discussions between the HI NBS Program and the Oregon State Public Health Laboratory to ensure correct identification and interpretation of VLCADD results on the HI NBS panel; (2) aid HI’s clinical genetics professionals in their discussions with parents regarding “abnormal” NBS results for VLCADD when newborns have a 1226C>T mutation; and (3) contribute to the current knowledge of the 1226C>T mutation and its classification as a pathogenic variant.

References:

Assuring Access to Nutritional Treatment for Inborn Errors of Metabolism: Michigan's Diet for Life Work Group Process and Experience

J. Bach, S. Lyon-Callo, D. Duquette, K. Tomasko and L. Gorman, Michigan Department of Community Health, Lansing, MI

Abstract

Background: Due to the success of newborn screening, the number of Michigan residents living with inborn errors of metabolism (IEM) is expected to double by 2030. In fall 2013, Genomics and Genetic Disorders staff at the Michigan Department of Community Health (MDCH) convened a work group to identify strategies for assuring access to nutritional treatment for patients of all ages with IEM.

Objectives: To identify and understand clinical guidelines for lifelong dietary treatment for individuals with IEM, describe facilitators and barriers to dietary compliance to assure best possible outcomes, recommend solutions that enable patients of all ages to receive appropriate treatment, and suggest long-term strategies for assisting families in obtaining coverage and reimbursement for metabolic foods.

Methods: Families of children with IEM and adult patients were invited to participate in the work group along with clinical experts; public health program staff representing NBS and other MCH programs; and Medicaid staff. Region 4 Midwest Genetics Collaborative provided assistance in planning and facilitating a series of 4 meetings.

Results: Seven priority components and more than 40 possible strategies were identified by work group members including the need to maintain a coordinated metabolic treatment program, educate families, and maximize use of third party insurance benefits for medical foods and other nutritional treatments. A summary report was made available for work group review before submission to the MDCH Public Health and Medical Services Administrations for feedback.

Conclusions: The work group process: 1) provided a forum for educating members about the complexity of treating IEM, the many barriers faced by families and providers, and current fiscal constraints of NBS funding; and 2) enabled development of an implementation plan and timeline based on input from key stakeholders. Continued involvement of families is a priority as suggested strategies are pursued.

Presenter: Janice Bach, MS, Michigan Department of Community Health, Lansing, MI, Phone: 517.335.8497, Email: bachj@michigan.gov

Summary

Background: Genetic inborn errors of metabolism (IEM) are rare, inherited disorders present at birth that affect how food is broken down in the body. If untreated, individuals with IEM develop severe medical problems such as failure to thrive, cognitive impairments, behavior problems, mental health issues, seizures, respiratory distress, coma or death. The State of Michigan mandated newborn screening for PKU in 1965; today, more than 50 different conditions are included on the newborn screening panel.
screening panel with over 30 requiring nutritional treatment. Through early diagnosis and treatment, individuals with IEM can lead healthy and productive lives.

The treatment for IEM is a lifelong, medically prescribed diet. For most metabolic disorders, protein intake from food must be severely restricted. A combination of strategies are used to limit intake of protein while providing substitute nutrients, frequently in the form of medical food or formula, low protein modified food, or amino acids and vitamin cofactors. Recommendations for treatment of IEM have evolved considerably over the decades. *Diet for Life* is currently known to be crucial for all individuals with IEM — regardless of age, gender or diagnosis.

Unlike many states, Michigan has no mandate for insurance coverage of metabolic nutritional treatments. Because metabolic formulas are classified as food by the FDA rather than drugs, coverage is not provided as a pharmacy benefit, and products must usually be obtained through a durable medical equipment supplier (DME). Due to difficulties with procurement and insurance reimbursement, the state Newborn Screening Program (NBS) has historically funded a designated metabolic clinic to coordinate follow-up and provide confirmatory diagnostic testing for babies with positive screens. The clinic also provides ongoing medical management, including distribution of medical formula (at no cost to families) for patients identified through screening.

In 2012, Michigan NBS spending began to exceed its annual fee-based revenue, and it became apparent that the current funding model for medical formula/food would not be sustainable. The cost of medical formulas alone increased from $141,000 in 1987 to $825,000 in 2013.

Contribution factors include:
- Diet for Life recommendation regardless of age or gender
- Increasing patient volume, projected to double by 2030
- Increasing number of disorders requiring diet treatment
- Increased laboratory and medical management costs
- Decreasing birth rate

A more comprehensive approach encompassing all forms of medical and low protein foods, and using existing sources of available insurance coverage, is needed. The challenge is to design an approach that does not create additional barriers, but instead sustains access to life-saving nutritional treatments that will optimize health outcomes for all patients with IEM.

**Objectives:** In the fall of 2013, Genomics and Genetic Disorders staff at the Michigan Department of Community Health (MDCH) convened the *Diet for Life Work Group* to identify strategies for assuring access to nutritional treatment for patients of all ages with IEM. The goals of the work group were to:

- Identify and understand existing clinical best practice guidelines for lifelong dietary treatment of individuals with IEM detected through newborn screening
• Describe facilitators and barriers to dietary compliance in order to assure the best possible outcomes for individuals with IEM
• Recommend feasible solutions that enable patients of all ages to receive appropriate metabolic formulas in light of Newborn Screening Program budgetary constraints
• Suggest long term strategies for assisting families in obtaining insurance coverage and reimbursement for metabolic foods

Methods: A letter was mailed to all known metabolic clinic patients receiving medical formula/food treatment, or their parents, inviting participation in the work group. Additional invitees included maternal child public health program staff representing newborn screening, Children’s Special Health Care Services (CSHCS) and WIC; Medicaid policy, managed care and medical consultant staff; clinical experts; and others concerned about barriers to maintaining necessary lifelong nutritional treatment. Staff from the HRSA-funded Region 4 Midwest Genetics Collaborative provided assistance with meeting coordination and planning; and served as neutral facilitators for the work group meetings.

Four meetings were held between October 2013 and January 2014. Approximately 50 individuals participated in one or more meetings, including about 20 individuals with IEM or their family members. At each meeting, 2-3 family representatives were asked to give a brief presentation on their experience living with IEM. The first meeting also included an explanation of the budget situation, background on metabolic disorders and diet for life recommendation, examples of diets for individuals with IEM, and the opportunity to sample metabolic formulas. The second and third meetings included review of definitions; funding sources and various state models; and brainstorming possible solutions for adults and children, respectively. The final meeting included discussion of the proposed model for Michigan and voting on key components with use of an audience response system to record results.

Results: By sharing diverse experiences and expertise, the group was successful in developing a common understanding of the complexities of treatment and reimbursement for IEM; the efforts of patients, families and clinical staff to use and maintain dietary therapies, and the tremendous impact of treatment on people’s lives. The process also helped to build stronger connections among MDCH, clinicians and families as well as between the MDCH Public Health and Medical Services Administrations. The need for a Michigan-specific approach was recognized, and work group members identified more than 40 possible strategies which were grouped into 7 overarching components that impact access to treatment for IEM. A majority of members agreed that all of the following components were very important to absolutely essential for assuring access to lifelong treatment:

1. A coordinated metabolic treatment program
2. Family education and advocacy
3. Maximum use of third party insurance benefits for medical foods and other nutritional treatments
4. Increased access to low protein modified foods
5. A safety net for people with no available coverage
6. Coordination with state and federal supplemental food programs
7. Possible legislation, if needed

A summary report of the work group’s findings was prepared and is available at [www.michigan.gov/IEMtreatment](http://www.michigan.gov/IEMtreatment). The report has been shared with MDCH Public Health and Medical Services Administration

officials, and is meant to inform decisions on the best ways to help assure that all Michigan residents with IEM have lifelong access to medical formula and other critical dietary therapies.

Conclusion: The Diet for Life Work Group process provided a forum for educating participants about the complexity of treating IEM, the many barriers faced by families and providers, and current fiscal constraints of NBS funding. Subsequently, these issues have become more visible and elevated to the highest levels of MDCH administration. Currently, NBS, CSHCS and Medicaid staff is working to implement strategies identified by the work group, such as addressing barriers to procurement of medical formula products through DMEs. Immediate next steps include collecting additional data on third party coverage by systematically recording attempted insurance billing, denials, appeals, co-pays and deductibles. Continued involvement of families is a priority, and a new work group will be formed to provide input from the family perspective as policies for insurance billing are developed and safety net provisions for all ages are established.

1Michigan Department of Community Health, Lansing, MI; 2Michigan Public Health Institute, Okemos, MI.