**Background & Objectives**

- Phenylalanine hydroxylase (PAH) deficiency is clinically heterogeneous
- The National Institutes of Health (NIH) has classified PAH deficiency into 5 categories of severity based on pre-treatment blood phenylalanine (phe) level:
  - < 5%: PAH deficiency (PAH-D) with Mild HPA
  - 5% to 10%: PAH deficiency (PAH-D) with Moderate HPA
  - 10% to 30%: PAH deficiency (PAH-D) with Severe HPA
  - 30% to 60%: PAH deficiency (PAH-D) with Very Severe HPA
  - > 60%: PAH deficiency (PAH-D) with Uncompensated HPA

**Methods**

- To describe variants identified in the PAH gene among a cohort of Canadian children with PAH deficiency
- To assess the genotype-phenotype associations of 112 PAH deficiency patients in Canada

**Participants**

- Children born between 2006 and 2015
- Receiving care for an inherited metabolic disease at one of 13 participating Canadian Hereditary Metabolic Diseases Treatment Centres

**Eligibility**

- Diagnosed with PAH deficiency
- Complete baseline data (demographic & diagnostic information)
- PAH genotype information identified (via molecular genetic testing or inference from sibling)

**Data collection**

- Database on RedCap
- Medical chart-abstacted data

**Measures**

- Max blood phe level in first 21 days of life
- Used to estimate pre-treatment blood phe levels and assign disease classification per NIH categories
- Sensitivity analysis conducted by comparing max blood phe in first year of life
- Prescribed dietary phe intake between age 2-3 years
- Used as a potential proxy for phe tolerance

**Analysis**

- Descriptive analysis of children with PAH deficiency in Canada

**Results & Interpretation: Descriptive Analysis & Max Blood Phenylalanine Levels**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Participants with PAH Deficiency (n=112)</th>
<th>Max Blood Phenylalanine Levels (μmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Birth</td>
<td></td>
<td>Total Max Blood Phenylalanine Levels (μmol/L)</td>
</tr>
<tr>
<td>2006</td>
<td>24</td>
<td>11%</td>
</tr>
<tr>
<td>2007</td>
<td>21</td>
<td>9%</td>
</tr>
<tr>
<td>2008</td>
<td>14</td>
<td>6%</td>
</tr>
<tr>
<td>2009</td>
<td>22</td>
<td>10%</td>
</tr>
<tr>
<td>2010</td>
<td>18</td>
<td>8%</td>
</tr>
<tr>
<td>2011</td>
<td>19</td>
<td>9%</td>
</tr>
<tr>
<td>2012</td>
<td>27</td>
<td>12%</td>
</tr>
<tr>
<td>2013</td>
<td>22</td>
<td>10%</td>
</tr>
<tr>
<td>2014</td>
<td>27</td>
<td>12%</td>
</tr>
<tr>
<td>2015</td>
<td>28</td>
<td>13%</td>
</tr>
</tbody>
</table>

| Table 1. Participant characteristics in the present study compared with all PAH deficiency participants enrolled in CIMDRN

**Participants with PAH genotype information:**

- 50% of all PAH deficiency participants in CIMDRN cohort have PAH genotype information
- Differences in proportion of participants with genotype information reflect the variation in availability and usage of molecular genetic testing across Canadian treatment centres and over time
- Genotype information was inferred from sibling data for 9 participants

**Max blood phenylalanine levels:**

- 58% of participants had a max blood phe level >600 μmol/L in first 21 days of life
- 19% of max blood phe levels in first 21 days of life came from newborn screening test results, not diagnostic tests
- When comparing disease classification based on max blood phe in first 21 days of life and max blood phe level in first year of life, <5 participants changed classifications

**Results & Interpretation: PAH Genotypes Identified**

- Genotypes identified through molecular genetic testing:
  - Alleles were classified according to their variant type in ClinVar® as of April 28th, 2019
  - 80 unique alleles were identified
  - Most common variant type: Missense (n=90, 61%)
  - Most common alleles: c.1222T>C (n=30, c.1315+164A>G=20), c.1347T>C (n=12)
  - 93 unique genotypes identified
  - Most common genotype classification: Missense/Missense (n=45, 48%)
  - 4 alleles were not reported in ClinVar® as of April 28th, 2019

**Table 2. Frequencies of PAH genotypes identified in the CIMDRN cohort

**Genotypes within each PAH deficiency classification:**

- 7 genotypes were found in more than 1 disease classification

**Prescribed dietary phe intake:**

- 30 participants did not have a metabolic clinic visit between age 2-3 years or were under 2 years old by end of study period
- 22% of included participants were prescribed an unrestricted diet at age 2-3 years
- 76% of those prescribed an unrestricted diet were classified as treated with BH4

- As expected, our data suggests that there is an inverse relationship between max blood phe in the first 21 days of life and prescribed dietary phe intake

**Conclusions & Next Steps**

- Better understanding of the genotype-phenotype relationship among children with PAH deficiency can inform expectations about disease severity and care needs, and may lead to improved management

- Next steps:
  - Harmonizing the collection and interpretation of data on prescribed dietary phe intake as a proxy indicator of phe tolerance

- Genotype-phenotype analysis for BH4 responsiveness

**References:**


**Figure 2. Phe Deficiency Classification based on max blood phe level in first 21 days of life for all patients with PAH deficiency (n=112)**

- Red = Moderate HPA
- Yellow = Severe HPA
- Green = Very Severe HPA
- Pink = Uncompensated HPA

**Figure 3. Participant Flow Diagram**

- Participants with PAH deficiency information in the CIMDRN cohort (n=112)

- Participants with PAH genotype information:
  - 50% of all PAH deficiency participants in CIMDRN cohort have PAH genotype information
  - Differences in proportion of participants with genotype information reflect the variation in availability and usage of molecular genetic testing across Canadian treatment centres and over time
  - Genotype information was inferred from sibling data for 9 participants

- When comparing disease classification based on max blood phe in first 21 days of life and max blood phe level in first year of life, <5 participants changed classifications

**Figure 4. PAH genotype classification**

- Red = Moderate HPA
- Yellow = Severe HPA
- Green = Very Severe HPA
- Pink = Uncompensated HPA

- As expected, our data suggests that there is an inverse relationship between max blood phe in the first 21 days of life and prescribed dietary phe intake

**Table 3. Distribution of PAH genotypes identified in the CIMDRN cohort

- Most common genotypes: c.1222T>C (n=30, c.1315+164A>G=20), c.1347T>C (n=12)
- 93 unique genotypes identified

- Most common genotype classification: Missense/Missense (n=45, 48%)