Constructing an atlas of the human metabolome to enable phenotyping, genome mapping and understanding genetic disease

Michael Milburn, Ph.D. - CSO, Metabolon, Inc.
Metabolon is the global leader in metabolomics

*Our technology is advancing life sciences research & improving health*

- Founded in 2002
- Over 180 employees worldwide with expertise in biochemistry, mass spectrometry and software development
- 54,000 sq. ft. facility in Research Triangle Park, NC & Sacramento
- CLIA-certified/CAP-accredited lab
- >5,000 studies, >800 clients worldwide, >700 publications
Metabolomics & molecular phenotyping

Risk of Disease
Genes suggest what might be

Actionable Information
to prevent, diagnose & treat disease

- 3 billion base pairs
- Ongoing discoveries of gene function
- Larger detailed data sets
- Improving clinical relevance

- Over 2,000 metabolites
- Biochemistry well defined
- Current health state
- Accounts for external factors (diet, environment, microbiota)

An integrative approach for deciphering the phenotype
Metabolomics
The key molecular phenotyping technology

**GENOMICS**
Our genes suggest what diseases we might be predisposed to, but it’s an incomplete picture of human health.

**LIFESTYLE/ENVIRONMENT**
External factors such as diet, exercise, medications, microbiota, and even where we live influence the state of our metabolome.

**PHENOTYPE**
A complete status of health that can be used to prevent, diagnose and treat disease.
Biomarkers
Mechanistic understanding
Drug MoA
Cellular characteristics

>4000 Studies
Institutional Knowledge
Expert Biochemists
~525 Publications

Discovery HD4™ platform launched in April 2014

Statistical Analysis

Eliminate Noise
Data Reduction

40,000 ion features
PT Mass MS/MS

40,000 ion features
QA/QC

UHPLC (HILIC)-MS/MS

UHPLC-MS/MS (+ESI) 1
UHPLC-MS/MS (+ESI) 2
UHPLC-MS/MS (-ESI)

Biomarkers
Mechanistic understanding
Drug MoA
Cellular characteristics

Interpretation
- >4000 Studies
- Institutional Knowledge
- Expert Biochemists
- ~525 Publications
Data quality continues to improve (RSDs in plasma)

<table>
<thead>
<tr>
<th>Year</th>
<th># metabolites in plasma</th>
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<tr>
<td>2005</td>
<td>(48)</td>
</tr>
<tr>
<td>2007</td>
<td>(18)</td>
</tr>
<tr>
<td>2009</td>
<td>(10)</td>
</tr>
<tr>
<td>2011</td>
<td>(10)</td>
</tr>
<tr>
<td>2013</td>
<td>(7)</td>
</tr>
<tr>
<td>2014</td>
<td>(&lt;5%)</td>
</tr>
<tr>
<td>2015</td>
<td>(&lt;4.5%)</td>
</tr>
</tbody>
</table>

Data coverage

Whole Metabolome Screening

- 0 to 500 metabolites
- 500 to 1000 metabolites
- 1000 to 2000 metabolites
- 2000 to 2500 metabolites
- 2500 to 3000 metabolites

Yearly # metabolites:

- '05: 4
- '06: 5
- '07: 10
- '08: 10
- '09: 15
- '10: 15
- '11: 15
- '12: 15
- '13: 20
- '14: 25
- '15: 30
- '16: 35

Metabolon’s Technology Continuously Improves
Innovations (2003 - 2016)
About 200 molecules are derived from bacterial metabolism

- Short chain FA:
  valerate
  Isovalerate
  Methylpropionate

- Lipids:
  Lyso-PC, lyso-PE
  Monacetylglucorol
  cholesterol

- Lipid metabolism

- Aromatic amino acid metabolism
  phenyllactate
  phenylacetate
  p-cresol sulfate
  3-(4-hydroxyphenyl)lactate
  4-hydroxyphenylpyruvate
  4-hydroxyphenylacetic acid
  3-hydroxyphenylacetic acid
  3,4-dihydroxyphenylacetic acid
  phenylacetylglutamine
  phenylacetylglycine
  2-(4-hydroxyphenyl)propionate
  3-(3-hydroxyphenyl)propionate
  3-(4-hydroxyphenyl)propionate
  3-phenylpropionate
  phenol sulfate
  4-hydroxyxinnamates
  indolelactate
  indoleacetate
  indole-3-carboxylic acid
  n-acetyltryptophan
  3-indoxyl sulfate
  indolepropionate
  skatol
  indoleacetyleglutamine

- Energy metabolism
  lactate
  formate, succinate
  glucose
  urea
  creatine
  creatinine
  ketoisovalerate

- Polyamine metabolism
  cadaverine
  putrescine
  spermidine
  spermine

- Riboflavin
  pyridoxine
  folate

- Vitamin metabolism

- Bile acid metabolism
  2nd bile acids:
  cholate
  dehydrocholate
  ursodeoxycholate
  deoxycholate
  glycodeloxycholate
  ketodeoxycholate
  glycolithocholate sulfate
  tauroliothocholate
  tauroliothocholate sulfate
  lithocholate
  diketolithocholate
  ketolithocholate
  hyocholate
  glycocholenate sulfate
  taurocholenate sulfate
  glycoursodeoxycholate
  tauroursodeoxycholate

- Xenobiotic metabolism

- Exclusively or mainly contributed by bacteria metabolism
- Contributed by both mammalian cells and bacteria

- Metabolites:
  hippurate
  2-hydroxyhippurate
  3-hydroxyhippurate
  4-hydroxyhippurate
  3-hydroxybenzoate
  4-hydroxybenzoate
  3,4-dihydroxybenzoate
  2,4,6-trihydroxybenzoate
  p-hydroxybenzaldehyde
  methyl-4-hydroxybenzoate
  3-(2-hydroxyphenyl)propionate
  vitexin
  daidzein
  genistein
Microbiota metabolites underlie autism phenotype

Background & objective
• In a mouse model of autism, alterations in microbiota were associated with an autistic phenotype & corrected by a probiotic treatment
• Goal was to determine the underlying mechanism?

Metabolomic data
4EPS highly elevated, reduced to normal by probiotic treatment
Hypothesis: 4EPS is mechanistically linked to autism phenotype

Conclusions
• Metabolites underlying microbiota potentiated autism symptoms
• Another illustration that metabolites frequently potentiate the myriad of effects that microbiota influence on mammalian physiology and disease

Key finding
4EPS induces autism phenotype in WT mice
Discovery HD4™ Platform

Extensive Metabolite Library

High resolution biochemistry surveys central metabolism & peripheral pathways that drive attributes of phenotype.

Biomarkers for:
- Oxidative stress
- Inflammation
- Mitochondrial function
- Signaling
- Cell trafficking
- Cell activation
- Methylation
- Gut microbiome
Atlas of the Human Metabolome

Helmholtz Zentrum München
King’s College London
Metabolon, Inc.
Key publications applying Metabolon’s metabolomics in large population genetic studies

- **Human metabolic individuality in biomedical and pharmaceutical research.** *Nature* **477**, 54-60 (2011)
- **Minning the Unknown: A Systems Approach to Metabolite Identification Combining Genetic and Metabolic Information.** *Plos Genetics* 8, e1003005 (2012)
- **Biomarkers for type 2 diabetes and impaired fasting glucose using a non-targeted metabolomics approach.** *Diabetes*, 62, 4270-4276 (2013)
- **Associations between Metabolomic Compounds and Incident Heart Failure among African-Americans: the Atherosclerosis Risk in Communities (ARIC) Study.** *American Journal of Epidemiology*, 178, 534-542 (2013)
- **Genome-Wide Association Study of a Heart Failure Related Metabolomic Profile Among African Americans in the Atherosclerosis Risk in Communities (ARIC) Study.** *Genet Epidemiol*. 37, 840-5 (2013)
- **Long term conservation of human metabolic phenotypes and link to heritability,** *Metabolomics*, 10, 1005-1017 (2014)
- **Human Metabolome Associates With Dietary Intake Habits Among African Americans in the Atherosclerosis Risk in Communities Study.** *American Journal of Epidemiology* ; 179, 1424-33 (2014)
- **Epigenetics meets metabolomics: an epigenome-wide association study with blood serum metabolic traits.** *Hum. Mol. Genet.*, 23, 534-545 (2014)
- **Novel genetic associations with serum level metabolites identified by phenotype set enrichment analyses.** *Hum. Mol. Genet.*, 23, 5841-5857 (2014)
- **Whole genome sequencing identifies common, low-frequency, and rare variants associated with human blood metabolome.** *Nature Genetics*, in press
Genetic Origins of Individual Variations in Metabolism

More than 100 years ago, Archibald Garrod already suggested a link between chemical individuality and predisposition to disease.
Concordance Between Cohorts

Association with Metabolite Concentration Ratios

- = p-values that are plotted out of range

Associations with metabolite concentrations (not shown) demonstrated similar concordance.
Study Results (Nature Genetics, 46, 543-550, 2014)

Medical and pharmacological relevance of metabolomic associations

- 36 genes linked to complex disease traits or drug responses
- 10 genes are targets of 45 drugs
- Rest are targets of ~400 drugs in development
- Involvement in other aspects of human health and disease
- 26 genes associated with IEMs
- Potential for novel biomarkers

<table>
<thead>
<tr>
<th>Gene</th>
<th>Metabolic locus (bold = novel association in this study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dev</td>
<td>Compound in development (preclinical, Phase I-III, preregistered or registered)</td>
</tr>
<tr>
<td>b</td>
<td>Bio-active drug-like compound in ChEMBL</td>
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</table>
## Match Between Gene Function & GIM

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Associates With…</th>
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<tbody>
<tr>
<td>SCD</td>
<td>delta-9 fatty acid desaturase</td>
<td>C16:0 / C16:1</td>
</tr>
<tr>
<td>FADS1</td>
<td>delta-5 fatty acid desaturase</td>
<td>C20:3 / C20:4</td>
</tr>
<tr>
<td>PRODH</td>
<td>proline dehydrogenase</td>
<td>proline</td>
</tr>
<tr>
<td>GLS2</td>
<td>glutaminase 2</td>
<td>glutamine</td>
</tr>
<tr>
<td>OPLAH</td>
<td>5-oxoprolinase</td>
<td>5-oxoproline</td>
</tr>
<tr>
<td>PHGDH</td>
<td>serine biosynthesis</td>
<td>serine</td>
</tr>
<tr>
<td>IVD</td>
<td>isovaleryl-CoA dehydrogenase</td>
<td>isovaleryl carnitine</td>
</tr>
<tr>
<td>NT5E</td>
<td>5'-nucleotidase</td>
<td>inosine</td>
</tr>
<tr>
<td>ACE</td>
<td>peptidyl-dipeptidase</td>
<td>dipeptides</td>
</tr>
<tr>
<td>NAT8</td>
<td>N-acetyltransferase</td>
<td>N-acetylornithine</td>
</tr>
</tbody>
</table>

In the examples shown, the metabolite is a substrate or product of the enzyme encoded by the gene listed.
Concordance Between Cohorts

SCAD Locus & Butyrylcarnitine:Propionylcarnitine

- SCAD is a key enzyme β-oxidation.
- P-value<10^{-305}
- Increased levels of short-chain acylcarnitines are diagnostic for SCAD deficiency.

NAT8 Locus & N-acetylornithine

- N-acetyltransferase function of NAT8 matches the associating metabolite N-acetylornithine.
- Association with glomerular filtration and CKD.
A Snapshot of Biochemical Concentrations Can Phenotype The System

Since biology is driven to maintain metabolic homeostasis

- Whether a phenotype is driven by a single mutation or a combination of genetic differences, environmental influences or the microbiota, metabolism provides a systems-level diagnostic.
Whole genome sequencing identifies common, low-frequency, and rare variants associated with human blood metabolome

*Nature Genetics, in press*

1,960 twins on three time points

whole genome sequencing

metabolomics

mapping gene variance to metabolite levels
Heritability of serum metabolites and their associations with high and low frequency mutations

- 644 metabolites have consistent heritability (h² > 0.6: 136 metabolites, h² > 0.3: 427 metabolites)
- 246 metabolite associations mapped to common and low frequency variant (90 novel findings).
  New insights on biomarkers and pathways associated with various diseases.
Mapping Rare Mutations

- 17 metabolite associations mapped to 347 rare gene variants, affecting ~10% of the study population.
- The detected metabolic abnormalities were the results of heterozygous rare variants on inborn errors of metabolism, commonly accepted as autosomal recessive diseases.
Dimethylglycine and DMGDH

<table>
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<tr>
<th>BIOCHEMICAL</th>
<th>SUPER.PATHWAY</th>
<th>SUB.PATHWAY</th>
<th>heritability</th>
<th>GWAS.loci</th>
<th>pathway.genes</th>
<th>OMIM.gene</th>
<th>rare.func.gene</th>
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<tr>
<td>dimethylglycine</td>
<td>Amino Acid</td>
<td>Glycine, Serine and Threonine</td>
<td>0.75</td>
<td>DMGDH</td>
<td>BHMT2, BHMT,</td>
<td>DMGDH</td>
<td>DMGDH</td>
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<tr>
<td></td>
<td></td>
<td>Metabolism</td>
<td></td>
<td></td>
<td>D</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Outlier twins</th>
<th>genotype</th>
<th>MAF</th>
<th>variant</th>
<th>function</th>
<th>mutation</th>
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<tr>
<td>15821;15822</td>
<td>0/1</td>
<td>2/3918</td>
<td>chr5_79021608_T_G</td>
<td>stop_lost</td>
<td>12/12</td>
</tr>
<tr>
<td>15821;15822;33381;33382</td>
<td>0/1</td>
<td>16/3918</td>
<td>chr5_79044400_G_A</td>
<td>missense</td>
<td>6/16</td>
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<tr>
<td>56031;56032</td>
<td>0/1</td>
<td>4/3918</td>
<td>chr5_79033302_T_A</td>
<td>stop_gained</td>
<td>8/16</td>
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</table>
Short-chain Acyl-CoA Dehydrogenase and Ethylmalonate
Gene penetrance: 3905

- High sorbitol and fructose level, indicating that fructose metabolism was disrupted in this subject.

- WES sequencing priority list from computer analysis did not report an aldolase B mutation.

- We recommended a careful review of the sequencing data for ALDOB. A mutation was found that could account for the patient showing signs of fructose intolerance.

- Patient was called in and dietary planning recommended as persistent fructose intolerance can lead to various adverse symptoms including damages to liver and kidney.
Gene penetrance: 3923

- 3923 carried a mutation in xanthine dehydrogenase in the purine degradation pathway. HGMD reports this allele (CM128354) as having a high confidence association with xanthinuria type I.
- Patient was diagnosed with xanthinuria and placed on dietary intervention.
- Xanthine metabolism was entirely normal on Patient 3923 suggesting that the potential xanthinuria allele had no impact on the purine degradation pathway in this subject.
Sensitivity to acetaminophen-induced toxicity

2-hydroxyacetaminophen sulfate
2-methoxyacetaminophen sulfate
3-(cystein-S-yl)acetaminophen
4-acetaminophen sulfate
4-acetamidophenol
p-acetamidophenylglucuronide
glycocholate
glycochenodeoxycholate
taurocholate
taurochenodeoxycholate

3976
3958

28
Clinical Applications

Clinical Diagnostic Tests
- Quantose IR
- Quantose IGT
- accuGFR

Precision Medicine
- Meta IMD
- GHA
- Undiagnosed Disease
- Gene Penetrance Assessment

LC/MS platform

HD4 platform
Inborn Errors of Metabolism

Dr. Art Beaudet, Baylor College of Medicine
Design of study

• 200 patients - blood and urine samples were sent to Metabolon blinded

• Some with defined disease and some previously determined unaffected

• Challenge: run them through the platform and determine who is diseased and who is unaffected, and determine what disease they have
Correct disease assessment

<table>
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<tr>
<th>Disorder</th>
<th>Specimens</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tr>
<td>3-Methylcrotonyl-CoA carboxylase (3_MCC)</td>
<td>4</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Argininosuccinic acid lyase (AL)</td>
<td>2</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Argininemia</td>
<td>4</td>
<td>100%</td>
<td>100%</td>
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<td>Cobalamin-related</td>
<td>6</td>
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<td>100%</td>
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<td>Citrullinemia</td>
<td>9</td>
<td>100%</td>
<td>100%</td>
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<td>Carnitine palmitoyltransferase II (CPT II)</td>
<td>1</td>
<td>100%</td>
<td>100%</td>
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<td>Glutaric aciduria type 1 (GA type1)</td>
<td>5</td>
<td>100%</td>
<td>100%</td>
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<td>3-OH-3-methylglutaryl (HMG) Co-A lyase</td>
<td>2</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Holocarboxylase</td>
<td>1</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Homocystinuria</td>
<td>2</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Isovaleric aciduria</td>
<td>2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Lysinuric protein intolerance (LPI)</td>
<td>2</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Maple syrup urine disease (MSUD)</td>
<td>18</td>
<td>100%</td>
<td>100%</td>
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<td>Medium chain acyl-CoA dehydrogenase (MCAD)</td>
<td>2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Methylmalonic aciduria (MMA)</td>
<td>9</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Ornithine transcarbamoylase (OTC)</td>
<td>19</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Propionic aciduria (PA)</td>
<td>9</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Phenylketonuria (PKU)</td>
<td>8</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Thymidine phosphoylase (MNGIE)</td>
<td>2</td>
<td>100%</td>
<td>100%</td>
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<tr>
<td>Trimethyllysine hydroxylase epsilon (TMHLE)</td>
<td>4</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Very-long chain acyl-CoA dehydrogenase (VLCAD)</td>
<td>2</td>
<td>50%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Maple Syrup Urine Disease

\[ a(A) + b(B) + c(C) + d(D) + e(E) + f(F) + g(G) + h(H) + i(I) + j(J) + k(K) = \text{Disease score} \]
Phenylketonuria Disease

J. Inherited Metabolic Disease
Patient 1 is the most affected in multiple analytes suggesting a more severe form of argininemia. Patient had been admitted 3 times in past three months due to acute decompensation associated with hyperammonemic events. Other patients had no acute events. Effect is not seen in arginine, but in other more distal biomarkers.
Isovaleric Acidemia

Leucine → 2-ketoisocaproic acid

- 2-ketoglutarate transaminase

Isovaleryl-CoA

- Isovalerylglycine
- Isovalerylcarnitine

3-methylcrotonyl-CoA

- 3-methylcrotonylglycine
- 3-Hydroxyisovalerate
- Hydroxyisovaleryl carnitine
- 3-methylglutarate
- 3-methylglutaryl carnitine
- 3-methylglutaconate

3-methylcrotonyl-CoA
decarboxylase

- ATP, HCO₃
- ADP

3-methylglutaconyl-CoA
dehydrogenase

- Oxidation
- De-esterification

3-hydroxyisovalerate

3-hydroxy-3-methylglutaryl-CoA

- HMG-CoA Lyase

Acetoacetate Acetyl-CoA
3-methylcrotonyl CoA carboxylase deficiency

Leucine → 2-ketoisocaproic acid
- 2-ketoglutarate transaminase

2-ketoisocaproic acid → Isovaleryl-CoA
- BCAA ketoacid Decarboxylase
- Glycine-N-acylase
- Acyltransferase

Isovaleryl-CoA → Isovaleryl-CoA
- Isovaleryl-CoA Dehydrogenase

Isovaleryl-CoA → Isovaleryl-glycine
- Oxidation De-esterification

Isovaleryl-CoA → Isovaleryl carnitine

Isovaleryl-CoA → Isovalerate

Isovaleryl-CoA → 3-hydroxyisovalerate

3-methylcrotonyl-CoA → 3-methylcrotonyl glycine
- 3-Hydroxyisovalerate
- Hydroxyisovaleryl carnitine
- 3-methylglutamate
- 3-methylglutaryl carnitine
- 3-methylglutaconate

3-methylcrotonyl-CoA → 3-methylcrotonyl-CoA carboxylate

3-methylcrotonyl-CoA carboxylate → 3-methylglutaconyl-CoA
- ATP, HCO₃
- ADP
- 3-methylglutaconate

3-methylglutaconyl-CoA → 3-hydroxy-3-methylglutaryl-CoA
- HMG-CoA Lyase

3-hydroxy-3-methylglutaryl-CoA → AcetoacetateAcetyl-CoA

3-methylglutaconyl-CoA → 3-methylglutaryl carnitine
Algorithm – Identification of specific disease signatures

• An algorithm was developed to identify those with isovaleric acidemia based on the biomarkers identified in the cohort study.
• Subjects
  – Blue = Affected individuals.
  – Black = Normals
  – Red = Isovaleric Acidemia subjects
  – Green = 3-MCC subjects
• The algorithm could identify those subjects with isovaleric acidemia, the normal, and differentiate the isovaleric acidemia subjects from the 3-MCC subjects.
Results

- 70 unaffected cases were scored as unaffected
- 129 of 130 diseased were called correctly
- The one patient missed was on therapy and not showing symptoms
Whole exome sequencing and metabolomic analyses as complements for diagnosis

METABOLOMIC PROFILING FOR DNA VARIANTS OF UNKNOWN SIGNIFICANCE (VUS)
Case Study

- Clinical presentation and family history:
  - Developmental delay
  - Intellectual disability, speech delay
  - Static encephalopathy and epilepsy (seizures with onset at birth)
  - Mild ataxia
- Prior work-up: Normal CMA, normal metabolic tests
- Exome sequencing revealed variants in SLC13A5:
  - c.997C>T (p.R333X) pathogenic variant
  - c.680C>T (p.T227M) predicted pathogenic variant
- SLC13A5 is a sodium/dicarboxylate cotransporter
  - Translocates Krebs cycle intermediates such as succinate, citrate, and alpha-ketoglutarate across plasma membranes
Metabolomic analysis confirms exome findings of citrate transporter deficiency.

EXOME findings
- *trans* mutations in SLC13A5
  - c.997C>T (p.R333X)
  - c.680C>T (p.T227M)
- Disorder: citrate transporter def.

Citrate

TCA cycle
Citrate transporter deficiency: plasma metabolomics

Citrate

(Succinate + Fumarate + Malate)

\[ P = 3.5 \times 10^{-6} \]

\[ P = 6.9 \times 10^{-6} \]
Meta IMD Report

<table>
<thead>
<tr>
<th>Meta IMD™ Disorders Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolites out of Expected Range</strong></td>
</tr>
<tr>
<td>3-hydroxyisovaleric acid</td>
</tr>
<tr>
<td>3-oxothiazolidine-4-carboxylic acid (3-OTC)</td>
</tr>
<tr>
<td>8-oxo-9-oxodecanoic acid (8-oxo-9-OD)</td>
</tr>
<tr>
<td>5-oxo-6-oxodecanoic acid (5-OT)</td>
</tr>
<tr>
<td>3-hydroxyisovaleric acid</td>
</tr>
</tbody>
</table>

**Meta IMD™ INHERITED METABOLIC DISORDERS**

Metabolics from Top Affected Pathways:
- alpha-hydroxybutyric acid
- 2-methyl-3-furanpropanoic acid
- 3-hydroxyisovaleric acid
- 2-methyl-3-furanpropanoic acid
- 4-methyl-3-oxobutanoic acid
- 5-oxo-6-oxodecanoic acid (5-OT)
- 3-hydroxyisovaleric acid

Metabolic Pathway Enriched with Metabolites Outside of Expected Range: Branched-Chain Amino Acid Metabolism

**Laboratory Comments:** None

**Findings:**
- The metabolites identified as outside the expected range all relate to branched-chain amino acid (BCAA) metabolism. Published biomedical literature suggests that levels of these metabolites are altered in BCAA disorders, such as Maple Syrup Urine Disease (MSUD), Erythro-CoA hydrolase, short-chain 3-hydroxyacid dehydrogenase (SC3HAD) deficiency, or 3-hydroxyisobutyryl-CoA dehydrogenase (3-HIBCD) deficiency.
- 12 of 15 metabolites in BCAA metabolism associated with MSUD were outside of the expected range.
- 2 of 15 metabolites in BCAA metabolism associated with MSUD were inside the expected range.
- 1 of 15 metabolites in BCAA metabolism defined as rare and associated with MSUD was detected.
- 2 of 2 metabolites in BCAA metabolism associated with MIMD deficiency were outside the expected range.
- 1 of 1 metabolite in BCAA metabolism associated with 3-HIBCD deficiency was outside the expected range.
- Ally-alanine is a rare metabolic defect (see Limitations, back page) that was detected.