How much more can we explain with genetics?
EHR mining and the undiagnosed patient

Lisa Bastarache
Future of Individualized Medicine, 2019
What is wrong with this patient?

- Hearing loss
- Numbness
- Auditory neuropathy syndrome
- Muscle spasms/neuropathy
- Wheelchair
- Dysphagia
- PEG tube
- Respiratory failure
- Intubated
- Blurry vision

Numbers:
- 32
- 33
- 34
- 35
- 36
# BROWN-VIALETTO-VAN LAERE SYNDROME

## HEAD & NECK
- **Ears**
  - Hearing loss, sensorineural
  - Absent brainstem auditory-evoked responses
- **Eyes**
  - Visual loss

## RESPIRATORY
- Respiratory insufficiency

## MUSCLE, SOFT TISSUES
- Muscle weakness, proximal, distal, and axial, severe
- Neurogenic changes seen on EMG
- Fibrillations

## NEUROLOGIC
- **Central Nervous System**
  - Cranial nerve palsies
  - Loss of independent ambulation
- **Peripheral Nervous System**
  - Axonal sensorimotor neuropathy

## LABORATORY ABNORMALITIES
- Abnormal acylcarnitine profiles

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**SLC52A2 or SLC52A3**

Riboflavin transport deficiency
A diagnosis, the old fashioned way

- Hearing loss, Numbness
  - Auditory neuropathy syndrome
    - Blurry vision
  - Muscle spasms/neuropathy
    - Wheelchair
    - Dysphagia
      - PEG tube
    - Respiratory failure
      - Intubated
- Begin riboflavin megadose
  - Regains sensation
  - Walks without walker
- Riboflavin challenge
  - Test abnormal
MCAD deficiency test

ACADM carrier 0.3% AF

Dx: MCAD def
Rx: L-carnitine

But…. No hypoglycemia
Wrong inheritance pattern

nucSEEK panel

CACNA1S VUS

KCNE1 VUS

Hypokalemic periodic paralysis

Phenotype doesn't fit

Normal ECG x3

Holter monitor unremarkable

19 candidate variants

We are very far from a world in which we can sequence patients’ genomes and easily interpret their risk of disease…
Rehm et al, NEJM 2015
Why don't we know more?
Phenotype risk score (PheRS)
A method to create Mendelian disease phenotypes
• Uses EHR data (billing codes)
• Enables a population level scan of Mendelian disease variants
MARFAN SYNDROME

HEAD & NECK
  Eyes
    - Retinal detachment
    - Iris hypoplasia

CARDIOVASCULAR
  Heart
    - Aortic regurgitation
  Vascular
    - Aortic root dilatation
    - Aortic dissection

SKELETAL
  Limbs
    - Joint hypermobility

CHEST
  Ribs
  Sternum
  Clavicles & Scapulae
  - Pectus excavatum

RESPIRATORY
  Lung
    - Pneumothorax

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Pectus excavatum
Joint dislocation
Pneumothorax
Retinal detachment

Aortic aneurysm

No Marfan symptoms
You can differentiate individuals diagnosed with Marfan syndrome using only the features of the disease.
## Phenotype risk scores identify patients with unrecognized Mendelian disease patterns

<table>
<thead>
<tr>
<th>Gene</th>
<th>Variant</th>
<th>rsID</th>
<th>OMIM</th>
<th>Phenotype categories in PhenoRS</th>
<th>Beta</th>
<th>P</th>
<th>ClinVar</th>
<th>HGMD</th>
<th>ACMG</th>
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<tbody>
<tr>
<td>CFTR</td>
<td>c.1529G&gt;T</td>
<td>rs11399389</td>
<td>1/27</td>
<td>Cryptic fibrosis</td>
<td>1.39</td>
<td>2.9 x 10^-6</td>
<td>P</td>
<td>Y</td>
<td>P</td>
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<tr>
<td>CHRNA4</td>
<td>p.Arg481Gln</td>
<td>rs58851425</td>
<td>1/21</td>
<td>Nocturnal frontal lobe epilepsy, 1</td>
<td>0.58</td>
<td>9 x 10^-6</td>
<td>U</td>
<td>U</td>
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<tr>
<td>DGKE</td>
<td>p.Trp325Leu</td>
<td>rs13802463</td>
<td>1/14</td>
<td>Nephrotic syndrome, type 7</td>
<td>1.31</td>
<td>6.1 x 10^-7</td>
<td>LP</td>
<td>Y</td>
<td>LP-P</td>
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<tr>
<td>SLC3A4</td>
<td>p.Asp948Asp</td>
<td>rs20065148</td>
<td>0/24</td>
<td>Sulfocystinuria</td>
<td>0.82</td>
<td>6 x 10^-5</td>
<td>U</td>
<td>U-P</td>
<td>U-P</td>
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<tr>
<td>CTH</td>
<td>p.Q124X</td>
<td>rs74572051</td>
<td>0/12</td>
<td>Cystic fibrosis</td>
<td>1.31</td>
<td>6.1 x 10^-7</td>
<td>U</td>
<td>U-P</td>
<td>U-P</td>
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<tr>
<td>KIF1B</td>
<td>p.Arg797Cys</td>
<td>rs12757498</td>
<td>0/21</td>
<td>Charcot-Marie-Tooth disease, 2A1</td>
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<tr>
<td>VWF</td>
<td>p.Asp1107Val</td>
<td>rs14037210</td>
<td>0/21</td>
<td>Von Willebrand disease</td>
<td>0.53</td>
<td>8 x 10^-5</td>
<td>U</td>
<td>U</td>
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<tr>
<td>KIF1A</td>
<td>p.Thr723Pro</td>
<td>rs11029784</td>
<td>1/25</td>
<td>Spastic paraplegia-30</td>
<td>0.84</td>
<td>9 x 10^-6</td>
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<td>F10</td>
<td>p.Arg349X</td>
<td>rs140912700</td>
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<td>Factor X deficiency</td>
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<td>HFE</td>
<td>p.Glu369Asp</td>
<td>rs14031942</td>
<td>0/40</td>
<td>Hemochromatosis</td>
<td>1.08</td>
<td>4 x 10^-5</td>
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<td>Y</td>
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<tr>
<td>T3</td>
<td>p.Cys290X</td>
<td>rs15946357</td>
<td>0/69</td>
<td>Thyroid dysmorphogenesis</td>
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<td>6 x 10^-5</td>
<td>Y</td>
<td>U-P</td>
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<tr>
<td>SH2D1A</td>
<td>p.Glu411Glu</td>
<td>rs11266834</td>
<td>0/22</td>
<td>Familial erythrocytosis, 1</td>
<td>1.48</td>
<td>8 x 10^-5</td>
<td>U</td>
<td>U-P</td>
<td>U-P</td>
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<tr>
<td>SPTBN2</td>
<td>p.Glu265Glu</td>
<td>rs14000265</td>
<td>0/11</td>
<td>Spinocerebellar ataxia</td>
<td>0.75</td>
<td>9 x 10^-5</td>
<td>U</td>
<td>U-P</td>
<td>U-P</td>
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<tr>
<td>FAN1</td>
<td>p.Arg630Glu</td>
<td>rs10238034</td>
<td>0/34</td>
<td>Intestinal nephritis, karyomegagic</td>
<td>0.15</td>
<td>9 x 10^-5</td>
<td>U</td>
<td>U</td>
<td>U</td>
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<tr>
<td>PANK2</td>
<td>p.Asp297Glu</td>
<td>rs13735925</td>
<td>0/26</td>
<td>HARP syndrome</td>
<td>0.58</td>
<td>1 x 10^-4</td>
<td>P</td>
<td>Y</td>
<td>P</td>
</tr>
<tr>
<td>SH2B3</td>
<td>p.Lys366Arg</td>
<td>rs14086876</td>
<td>0/22</td>
<td>Essential thrombocytopenia</td>
<td>0.33</td>
<td>8 x 10^-4</td>
<td>U</td>
<td>Y-P</td>
<td>U-P</td>
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<tr>
<td>AGT</td>
<td>p.Del555del</td>
<td>rs15406681</td>
<td>1/33</td>
<td>Primary hyperoxaluria, type I</td>
<td>0.92</td>
<td>1.7 x 10^-4</td>
<td>U-LB</td>
<td>L-B-U</td>
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<tr>
<td>PLCD1</td>
<td>p.Ala253Val</td>
<td>rs17024974</td>
<td>0/10</td>
<td>Familial cold autoinflammatory syn. 3</td>
<td>0.70</td>
<td>9 x 10^-5</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
</tbody>
</table>

- **Tested**: 6644 variant/disease pairs
- **Found**: 18 significant associations
Do patients with X variant have a higher PheRS?

**eMERGEseq**

- 15,000 patients sequenced for 109 genes
- 9 clinical sites
- Demographics, billing codes, sequence
High-throughput *FBN1* variant readout

**Pathogenic**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Score</th>
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<tbody>
<tr>
<td>p.C2552X</td>
<td>3.3</td>
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<tr>
<td>p.R1539X</td>
<td>3.1</td>
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<tr>
<td>p.N1463S</td>
<td>4.2</td>
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<tr>
<td>p.R3X</td>
<td>5.9</td>
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<tr>
<td>p.L1390fs</td>
<td>3.2</td>
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</tbody>
</table>

**Benign**

<table>
<thead>
<tr>
<th>Variant</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.L2815L</td>
<td>-0.2</td>
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<tr>
<td>p.Q2296Q</td>
<td>0</td>
</tr>
<tr>
<td>p.D2285D</td>
<td>0</td>
</tr>
<tr>
<td>p.A2028S</td>
<td>0</td>
</tr>
<tr>
<td>p.N1282S</td>
<td>0.4</td>
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<tr>
<td>p.P1148A</td>
<td>0.1</td>
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<tr>
<td>p.D964D</td>
<td>0.4</td>
</tr>
<tr>
<td>p.C685C</td>
<td>0.1</td>
</tr>
<tr>
<td>p.A52A</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Variants of Uncertain Significance
Two reasons patients remain undiagnosed.
Making a Cystic Fibrosis diagnosis, not just for pediatricians anymore

Age of CF diagnosis is increasing!

Atypical CF diagnosis by decade
Hearing loss, Numbness
Auditory neuropathy syndrome
Blurry vision
Muscle spasms/tremors, Wheelchair
Dysphagia, PEG tube
Respiratory failure, Intubated

PheRS = 14.1