UAB UNDIAGNOSED DISEASE PROGRAM

Bruce R. Korf, MD, PhD
Department of Genetics
UAB Personalized Medicine

- Genome Sequencing
- Pharmacogenetics
NIH Undiagnosed Disease Program

Review  Consultation  Sequencing

Mark Gourley  MARKEL  Did a DNA analysis of Silvia's blood cells.

Colleen Wahl  NURSE PRACTITIONER  Coordinated the medical team visits.

Maria Turner  DERMATOLOGIST  Looked for skin pigment changes under ultraviolet light.

Thomas Martello  CLINICAL GENETICIST  Performed an oral evaluation.

William Gafi  GIAB DENTIST  Performed an oral evaluation.

Lakshmi Gopal  GASTROENTEROLOGIST  Reviewed Silvia's gastrointestinal system, endoscopies and biopsies.

Adeline Ge  ACUPUNCTURE CONSULTANT  Gave Silvia an acupuncture treatment.

Galina Nesterova  CLINICAL GENETICIST  Looked for mutations in Silvia's physical measurements.
Table 1 Direct identification of the gene for a mendelian disorder by exome resequencing

<table>
<thead>
<tr>
<th>Filter</th>
<th>Kindred 1-A</th>
<th>Kindred 1-B</th>
<th>Kindreds 1+2</th>
<th>Kindreds 1+2+3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dominant</td>
<td>Recessive</td>
<td>Dominant</td>
<td>Recessive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(A+B)</td>
<td>(1+2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NB/SSV/</td>
<td>4.670</td>
<td>2.863</td>
<td>4.687</td>
<td>2.859</td>
</tr>
<tr>
<td>Not in dbSNP129</td>
<td>641</td>
<td>102</td>
<td>647</td>
<td>114</td>
</tr>
<tr>
<td>Not in HapMap 29</td>
<td>898</td>
<td>123</td>
<td>923</td>
<td>128</td>
</tr>
<tr>
<td>Not in either</td>
<td>456</td>
<td>31</td>
<td>464</td>
<td>33</td>
</tr>
<tr>
<td>Predicted damaging</td>
<td>204</td>
<td>6</td>
<td>204</td>
<td>12</td>
</tr>
</tbody>
</table>

Ng, S., et al.  Nature Genetics 2010;42:30
The Diagnostic Odyssey

Try again

Clinical problem

Interpretation

Differential diagnosis

Genetic testing

Making a definitive diagnosis: Successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease

Elizabeth A. Wynter, PhD, Alan N. Homer, MD, PhD, Carol E. Stover, MD, Daniel Mekhjian, MD, Renato R. Bonucci, MD, Brennan Tucker, MD, James M. Scott, MD, Fredrick flute, PhD, Michael C. Tischler, MD, Ragan I. Fyer, MD, Wayne J. Beach, MD, Lynne Brodsky, MD, PhD, Latonya Mitchell, PhD, Maggie J. Arfa, MD, James T. Cooper, MD, David A. Murphy, PhD, David P. Byk, MD, Werner K. Happe, MD, John M. Berman, MD, PhD, Howard J. Jacob, MD.
The Incidentalalome

Figure. Percentage of Total Population With a False-Positive Test Result

As the number of tests increases to 10,000, the fraction of the population that has a false-positive test result increases to more than 60%. Any large-scale genomic panel is therefore likely to routinely report false-positive results. The data for this figure were generated by running a simulation in which a population of 100,000 was tested with 1 through 10,000 tests, each with a sensitivity of 100% and a false-positive rate of 0.01%. That is, 10 individuals with false-positive tests were randomly selected from the population for each test. Because some individuals could be selected more than once with a larger panel of tests, the increase in the number of individuals with false-positive test results is less than linear.

Secondary Findings

WGS WORKFLOW

When?
- Prenatal
- Neonatal
- Adulthood

Where?
- EHR
- Cloud
- Personal Device
- Cell Nucleus