How Genomics solves undiagnosed patients

This project receives funding from the European Union's Horizon 2020 research and innovation programme

Start date: January 2018, Duration: 5 years

Conflict of interest:
I declare no potential conflict of interest in relation to this presentation.
50% of all patients with a rare disease will not have a diagnosis after Whole Exome Sequencing. This limits access to appropriate health care.
* 50% of all patients with a rare disease will not have a diagnosis

30 Mio patients in Europe
15 Mio unsolved
* 50% of all patients with a rare disease will not have a diagnosis
* This limits access to appropriate health care

30 Mio patients in Europe
15 Mio unsolved
What to do with „Unsolved“

• 80% of RD patients have a genetic cause of their disease: > Strong Omics approach
What to do with „Unsolved“

• 80% of RD patients have a genetic cause of their disease: > Strong Omics approach

What to do when „Solved“

• Implement with European guidelines in a way that is helpful to patients
Resources and infrastructures

Core group of 4 European Reference Networks: ERN-RND, ERN-EURO-NMD, ERN-ITHACA, ERN-GENTURIS

Associated networks: 6 additional ERNs and 2 Undiagnosed Patient Programmes (Italy, Spain)

Existing RD infrastructures: RD-Connect/ELIXIR, Orphanet, HPO, EuroGentest, Canadian Models and Mechanisms Network

Patient organisations: EURORDIS, Genetic Alliance UK
Resources and infrastructures

Core group of 4 European Reference Networks: ERN-RND, ERN-EURO-NMD, ERN-ITHACA, ERN-GENTURIS

Associated networks: 6 additional ERNs and 2 Undiagnosed Patient Programmes (Italy, Spain)

Existing RD infrastructures: RD-Connect/ELIXIR, Orphanet, HPO, EuroGentest, Canadian Models and Mechanisms Network

Patient organisations: EURORDIS, Genetic Alliance UK
Re-analysis of 19,000 exomes of unsolved cases
Re-analysis of **19,000** exomes of unsolved cases

800 ultra-rare RD patients presenting new phenotypes that will undergo WES/WGS

**WGS for 2,000 cases** to achieve a more complete coding sequence

**Novel omics approaches** (transcriptome, epigenome, proteome, metabolome, deep WES, deep molecular phenotyping) for more than **2,000 cases**

**Long-read genomes for 500 cases** with smartly chosen phenotypes such as anticipated repeat expansion disorders (SBMA; DM1 and DM2, disorders with phenotype anticipation)

**Multi-Omics approaches for 120 „unsolvable syndromes“**
Re-analysis of **19,000** exomes of unsolved cases

- **800 ultra-rare** RD patients presenting new phenotypes that will undergo WES/WGS
- **WGS for 2,000 cases** to achieve a more complete coding sequence
- **Novel omics approaches** (transcriptome, epigenome, proteome, metabolome, deep WES, deep molecular phenotyping) for more than **2,000 cases**
- **Long-read genomes for 500 cases** with smartly chosen phenotypes such as anticipated repeat expansion disorders (SBMA; DM1 and DM2, disorders with phenotype anticipation)

- **Multi-Omics approaches for 120 „unsolvable syndromes“**
Strategy to Solving the Unsolved

WES unsolved
WES Reanalysis
WGS + Other Omics

New candidate gene
Matchmaker + large cohorts
Functional validation
SOLVE-RD: Beyond the exome

The exome is only 1-2% of our entire genome
RNAseq in diagnostics
Discovery to Diagnostics

Modified from Shyr and Liu 2013
Solving the unsolved Rare Diseases

Coordinators: Olaf Riess, Holm Graessner (Tübingen)

Co- coordinators: Han Brunner (Nijmegen), Anthony Brookes (Leicester)

<table>
<thead>
<tr>
<th>Participant Nº</th>
<th>Participant Organisation Name</th>
<th>Short Name</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Eberhard Karls Universitaet Tuebingen</td>
<td>EKUT</td>
<td>Germany</td>
</tr>
<tr>
<td>2</td>
<td>Stichting Katholieke Universiteit Nijmegen</td>
<td>RUMC</td>
<td>Netherlands</td>
</tr>
<tr>
<td>3</td>
<td>University of Leicester</td>
<td>ULETIC</td>
<td>U.K.</td>
</tr>
<tr>
<td>4</td>
<td>University of Newcastle upon Tyne</td>
<td>UNEW</td>
<td>U.K.</td>
</tr>
<tr>
<td>5</td>
<td>Central Manchester University Hospitals NHS Foundation Trust</td>
<td>MUH</td>
<td>U.K.</td>
</tr>
<tr>
<td>6</td>
<td>Centre Hospitalier Region Universitaire Dijon</td>
<td>DIJON</td>
<td>France</td>
</tr>
<tr>
<td>7</td>
<td>Fundació Centre de Regulació Genòmica</td>
<td>CRG-CNAG</td>
<td>Spain</td>
</tr>
<tr>
<td>8</td>
<td>EURORDIS – European Organisation for Rare Diseases Association</td>
<td>EURORDIS</td>
<td>France</td>
</tr>
<tr>
<td>9</td>
<td>Institut National de la Sante et de la Recherche Medicale</td>
<td>INSERM</td>
<td>France</td>
</tr>
<tr>
<td>10</td>
<td>Univerzita Karlova</td>
<td>CUP</td>
<td>Czech Republic</td>
</tr>
<tr>
<td>11</td>
<td>European Molecular Biology Laboratory</td>
<td>EMBL-EBI</td>
<td>U.K.</td>
</tr>
<tr>
<td>12</td>
<td>The Jackson Laboratory Non Profit Corporation</td>
<td>JAX</td>
<td>USA</td>
</tr>
<tr>
<td>13</td>
<td>King’s College London</td>
<td>KCL</td>
<td>U.K.</td>
</tr>
<tr>
<td>14</td>
<td>University College London</td>
<td>UCL</td>
<td>U.K.</td>
</tr>
<tr>
<td>15</td>
<td>Universiteit Antwerpen</td>
<td>UA</td>
<td>Belgium</td>
</tr>
<tr>
<td>16</td>
<td>Universita degli Studi della Campania Luigi Vanvitelli</td>
<td>Uni Naples</td>
<td>Italy</td>
</tr>
<tr>
<td>17</td>
<td>Universita degli Studi di Ferrara</td>
<td>UNIFE</td>
<td>Italy</td>
</tr>
<tr>
<td>18</td>
<td>Universitaetsklinikum Bonn</td>
<td>UHB</td>
<td>Germany</td>
</tr>
<tr>
<td>19</td>
<td>IPATIMUP – Instituto de Patologia Eunmonologia Molecular da Universidade do Porto PCUP</td>
<td>UoP</td>
<td>Portugal</td>
</tr>
<tr>
<td>20</td>
<td>Academisch Ziekenhuis Groningen</td>
<td>UMCG</td>
<td>Netherlands</td>
</tr>
<tr>
<td>21</td>
<td>Charité – Universitätsmedizin Berlin</td>
<td>Charitié</td>
<td>Germany</td>
</tr>
</tbody>
</table>
How Genomics solves undiagnosed patients

This project receives funding from the European Union's Horizon 2020 research and innovation programme

Start date: January 2018, Duration: 5 years

Conflict of interest:
I declare no potential conflict of interest in relation to this presentation.