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.
The exome is only 1-2% of our entire genome!
UNSOLVED after WES:
50% of all patients with a rare disease will not have access to health care without having a clear diagnosis

300 Mio RD patients worldwide
150 Mio patients unsolved

30 Mio patients in Europe
15 Mio unsolved

3-4 Mio RD patients in Germany
1.5 Mio unsolved after WES
Limitations of Whole Exome Sequencing (WES)

Important: Type of enrichment system: SureSelectXT Human All Exon v6

Statistics of coverage:
- complete coding sequence +/-5bp intronic region
- depth of sequencing (at least 20 fold)
- coverage: 98.99%

Limitations of WES:
- Coverage
- Copy number
- Aberrant splicing
RNAseq in diagnostics

Improving genetic diagnosis in Mendelian disease with transcriptome sequencing
https://enhancer.lbl.gov/gallery_n.html
Disruptions of Topological Chromatin Domains Cause Pathogenic Rewiring of Gene-Enhancer Interactions

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B

Deletion B1
Deletion B2
Deletion B3

PAX3

Brachydactyly
B1 patient B2 patient

C

Inversion F1
WNT6

Duplication F2

F-syndrome
F1 patient F2 patient

D

Duplication P1

IHH

Dbf deletion

Polydactyly
P1 patient Dbf Mouse
PacBio sequencing reads

Read lengths > 20 kb
Data per SMRT Cell: 750 Mb - 1.25 Gb

- Half of data in reads: > 20 kb
- Top 5% of reads: > 30 kb
- Maximum read length: > 60 kb

From: http://www.pacificbiosciences.com
Technical hurdles in diagnostics

Implementation into diagnostics pathways

"Pilot diseases"
Challenge in Diagnostic Transition: From genome analysis towards „System Diagnostics“

Technological hurdles in diagnostics
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

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

**Novel omics approaches** (transcriptome, epigenome, proteome, metabolome, deep WES, deep molecular phenotyping) for more than **2.000 cases**

**Multi-Omics approaches for 120 „unsolvable syndromes“**
## Main implementation steps

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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
Solving the unsolved Rare Diseases

Coordinators: Olaf Riess, Holm Graessner (Tübingen)

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

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<th>Participant Nº</th>
<th>Participant Organisation Name</th>
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<td>EKUT</td>
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<td>Stichting Katholieke Universiteit Nijmegen</td>
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<td>8</td>
<td>EURORDIS – European Organisation for Rare Diseases Association</td>
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<td>Institut National de la Sante et de la Recherche Medicale</td>
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