Workshop genomDE

Herausforderung der Genomdiagnostik:
Seltene Erkrankungen

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Medical Need

UNSOLVED after WES:
>50% of all patients with a rare disease will not have access to health care without having a clear diagnosis

Not all monogenic disease genes known yet
Not all disease mechanisms known
Technical limitations
Limited target region sequenced
Epigenome?

300 Mio RD patients worldwide
150 Mio patients unsolved

30 Mio patients in Europe
15 Mio unsolved

Medical Need
Whole Genome Sequencing is the next logical consequence

3-4 Mio RD patients in Germany
1.5 Mio unsolved after WES
Potential der Genomsequenzierung

Genomics
- Point mutations
- Small InDels
- Copy number variations
- Structural variations
- Repeat expansions

Transcriptomics
- Aberrant expression
- Aberrant splicing
- Gene fusion

Epigenomics
- Methylation

Exome analysis
- Coding only

Short read Genome analysis
- „Complete“ genome
- „Complete“ genome
- „Complete“ genome
- Short repeats only

Long read Genome
- „Haplo-typing“
- Complete genome
- All repeat expansions

Pilot
- Short read
- Short read
- Cancer

Methylation
- Methylseq
- All in one?

Extend of contribution for SE unclear
Short read

Genome and Transcriptome

Missed by WES: Examples
Klinik:
Mammakarzinom (ED 30)

Kausale Varianten:

<table>
<thead>
<tr>
<th>Gen</th>
<th>Typ</th>
<th>Genotyp</th>
<th>Variante</th>
<th>Erbgang</th>
<th>Ausschlussgrund</th>
<th>gnomAD/NGSD hom/het</th>
<th>Kommentar 1</th>
<th>Kommentar 2</th>
<th>Auswerter</th>
<th>Klasse</th>
<th>In Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFE</td>
<td>missense variant</td>
<td>het</td>
<td>chr6:26093141-26093141 G&gt;A</td>
<td>n/a</td>
<td>Anderer (siehe Kommentare)</td>
<td>0.0383</td>
<td>27 / 1262</td>
<td>AR</td>
<td>3</td>
<td>nein (incidental finding)</td>
<td></td>
</tr>
<tr>
<td>RYR1</td>
<td>synonymous variant</td>
<td>het</td>
<td>chr19:39071036-39071036 G&gt;C</td>
<td>n/a</td>
<td>Anderer (siehe Kommentare)</td>
<td>0.0001</td>
<td>0 / 10</td>
<td>ACMG-VUS</td>
<td>3</td>
<td>nein (incidental finding)</td>
<td></td>
</tr>
</tbody>
</table>

Kausale CNVs:

<table>
<thead>
<tr>
<th>CNV</th>
<th>copy-number</th>
<th>Gene</th>
<th>Erbgang</th>
<th>Infos</th>
<th>Kommentar 1</th>
<th>Auswerter</th>
<th>Kommentar 2</th>
<th>Auswerter Klasse</th>
<th>In Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>chr17:41230209-41236209</td>
<td>AD</td>
<td>BRCA1, RPL21P4</td>
<td>regions: 6 size: 6.001kb</td>
<td>BIC, UMD, LOVD, Literatur pathogen</td>
<td>5</td>
<td>ja (diagnostic variant)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BRCA1 dupEx13 – Detection of a tandem duplication by genome analysis

(Tandem-) Duplikation

Ref.  
A  
B  
C

Subject  
A  
B  
B  
C

Ex14  
Bruchpunkt 1

Ex13  
Bruchpunkt 2

BRCA1 ENST357654
WGS in unsolved chorea acanthocytosis: Structural variants in VPS13A

Today >10% increase of diagnostic Sensitivity compared to WES
Larger Potential
Bedeutung des EU Netzwerkes für genomeDE
Implementation of a data re-analysis infrastructure

DATA ANALYSIS TASK FORCE WORKING GROUPS (WG)
- WG1 SNVs / indel
- WG2 CNVs
- WG3 RoH/relatedness
- WG4 de novo mutations
- WG5 Meta-analysis
- WG6 epigenomics
- WG7 RNAseq
- WG8 Somatic mutations
- WG9 Structural variants

DATA ANALYSIS TASK FORCE (DATF)
- Data analysis in tool-oriented working groups
- Develops novel tools
- Compiles existing tools

DATA INTERPRETATION TASK FORCE (DITF)
- Data interpretation in the disease context
- 1 DITF per ERN
- Defines disease groups / disease specific use cases
- Selects cohorts

WORKING GROUP
- Analysis Project X
  - Use Case 1
- Analysis Project Y
  - Use Case 2

TOOLS

Clinicians & geneticists

Cohorts
Unsolved cases

21,346 datasets collected from 20,807 individuals

Data Freeze 1: 7,447 datasets from 7,382 individuals
Data Freeze 2: 3,125 datasets from 3,070 individuals
Data Freeze 3: 10,774 datasets from 10,604 individuals

Data freeze 1+2 re-analysis (6,232 families)
745 newly solved families
11.95% SOLVED!
Potential der Genomsequenzierung

Strategische Diskussionspunkte
202 neonates: 45% neuromuscular, 22% respiratory, 18% immunologic/infect.

Trio-rGS: ~37% diagnostic yield

TAT: 7d

Metagenome: pathogenic microbes in 6 infants with symptoms of sepsis

(2 x Pseudomonas, Mycobact. Tuberculosis / h MastadenovirusB, h beta herpesvirus6A, h gamma herpesvirus4)

Wu et al. Application of full-spectrum rapid clinical genome sequencing improves diagnostic rate and clinical outcomes in critically ill infants in the China Neonatal Genomes project.

Critical Care Medicine 2021

21.07.2022

China Neonatal Genomes project
Repeat expansion Detection in srWGS diagnostics
Need for transcriptome analysis to complement WGS data
The GeMed diagnostic approach
Combining clinical genetics with genomic health

Why:
- Diagnostic sensitivity
- Automatization
- Data

Genome First
(Cancer syndromes, Rare Diseases)

Transcriptome („always“)
Pax tubes / blood

Disease causing mutation

Verified in Transcriptome?
- unsolved

Genome+

Exceptions: Clear
- Exempts
- Familial index patient

Exceptions: de novo
- ID/DD in children: Trio-Exome

ACMG73
5% aller WES/WGS

PRS
Breast Cancer
Diabetes Type 2
Ca. 2% each

Exceptions:
- Children
- Patients with psychiatric or neurodegenerative diseases

GeHealth
Prevention

Universitätsklinikum Tübingen
„Organisational Complexity“ of clinical care and diagnostic pathways in human genetics

Communication flow
- Patient’s autonomy
- Global informed consent

Sample flow
- Case Manager

Gene flow
- Genetic Nurse
- Clinical Geneticist
- Documentalist

Data flow
- Data base entries
- Data stewardship

Information flow
- Treatment decision
- Actionable genes
- Polygenic Risk Scores
- Biomarker
- RNAseq
- cfDNA
- DNA long read

Common diseases
- Genomic Health
- Newborn screening

Emerging new fields
- GHGA
- 1+MEGA
- MII
- ML/Al

Genomic Medicine – Olaf Riess
Structures to immediately enhance diagnostic sensitivity in RD

Strategic Discussion Points
Not data alone, but data interpretation and clinical integration are important!

**SOLVE-RD GERMANY / SOLVE-GD GERMANY**
- German DATF excellence network, coordinated interaction with German ERN-organized DITFs
- Technically sophisticated but diagnostically experienced NGS+ („multiOmics“)

**GD Diagnostic Competence Centers**
- Latest technologies, semiautomated, high throughput, interconnected, „accessible“

Integration in and interaction with: national ERNs, RD research networks, 1+MG, AI Genomics & MultiOmics
Need in diagnostic care of RD/GD: Data of unclear clinical implication: How to proceed?

- Variant Interpretation Data Base
  - Focus: Variants of unknown clinical significance; VUS class 3, expert networks

- Variant Validation Groups
  - Gene pathway focused experts experimentally validating VUS class 3

- German RDMM
  - Disease modeling network for ultra-rare diseases, establishing novel disease genes or novel disease mechanisms
I declare to receive an explorative grant from Illumina for implementation of WGS into clinical care.

I receive further funding for genome analysis from the EU and the German Research Foundation (NGS Competence Center).