Solve-RD

Solving the Unsolved Rare Diseases

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Solve-RD - Facts & Figures

The main ambitions of Solve-RD are (i) to solve large numbers of rare disease (RD), for which a molecular cause is not know yet, by sophisticated combined Omics approaches, and (ii) to improve diagnostics of RD patients through contribution to, participation in and implementation of a "genetic knowledge web" which is based on shared knowledge about genes, genomic variants and phenotypes. Solve-RD will pursue a clear visionary and integrated "beyond the exome" approach and will demonstrate strategies to identify disease causes in unsolved genetic RD patients as currently about 50% of all RD causes remain unclear.

Through its integrated approach focussing on identifying disease-causing mechanisms in patients who received WES with a negative or an inconclusive molecular diagnosis, Solve-RD will significantly increase the diagnostic yield from 50% to >70% by developing novel strategies using novel molecular approaches.

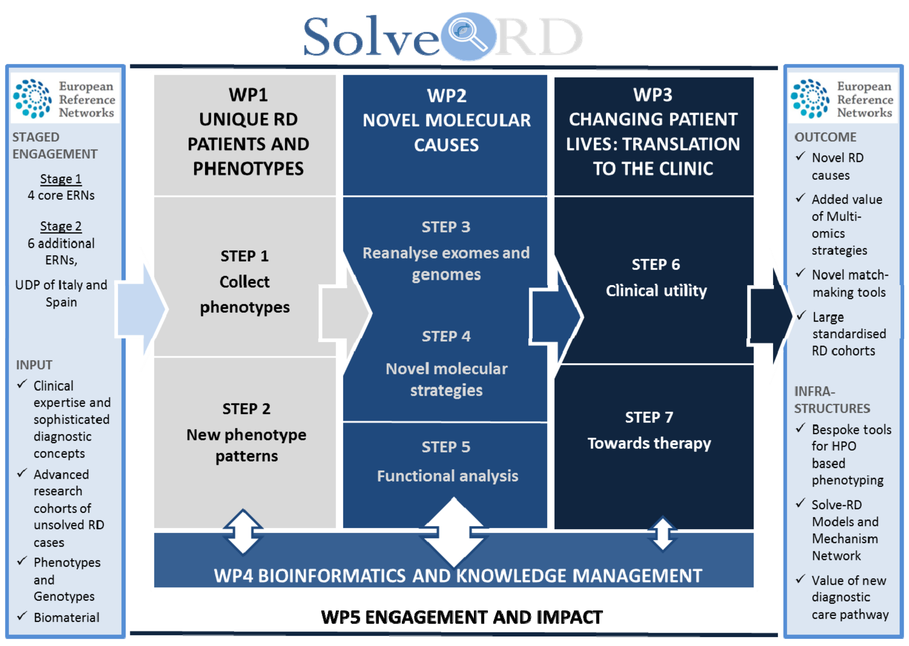
- EU-funding: 15 Mio. EUR under Horizon 2020
- Project duration: five years (1.1.2018 - 31.12.2022)
- Involves 4 European Reference Networks (ERNs) - the core ERNs: ERN-RND, ERN-EURO-NMD, ERN-ITHACA, ERN-GENTURIS
- Consortium comprises 21 partner from 10 countries:
  - Leading clinicians, geneticists and translational researchers of 4 core ERNs
  - RD research and diagnostic infrastructures (RD-Connect, Orphanet/ORDO, Human Phenotype Ontology [HPO], EuroGentest)
  - Patient organisations (EURORDIS, Genetic Alliance UK)
  - Leading experts in the field of –omics technologies, bioinformatics and knowledge management

Challenges

Challenge 1: Accessibility of unsolved RD cohorts with comprehensive genetic and phenotypic data ➔ WP1

Challenge 2: New and improved approaches for the discovery of novel molecular causes ➔ WP2

Challenge 3: Translate discoveries to impacting clinical practice ➔ WP3



Key Deliverables

- **Novel disease causing genes**
  Novel validated disease causing genes will be transferred to routine diagnostics
- **Novel diagnostic approaches**
  Applied in Solve-RD cohorts and scrutinised for clinical utility in Solve-RD
- **Ontology of unsolved rare diseases**
  Ontology sustainable and ready for uptake of further unsolved RD
- **Collection of phenotypic and genomic data from unsolved patients**
  High quality FAIR qualified data sustainably stored at RD-Connect and EGA
- **Evidence based methodology to communicate (gen)omics results**
  Methodology has been approved by a few ERNs and will need to be adapted by further ERNs
- **Trial-ready cohorts in registries and biobanks**
  Registries and biobanks are existing and will need to be exploited for trial design

Implementation Steps

STEP 1
Adapt tools for HPO-based collection of phenotypes of unsolved RD cases

Pool standardised information of a large number of unsolved RD cases from advanced research cohorts: phenotype and exome data, biomaterial and patient consent

STEP 2
Create an ontology of unsolved RD cases: Utilise novel algorithms to compare phenotypes from unsolved RD with phenotypes from solved RD and RD models

STEP 3
Standardised re-analysis of large number of existing unsolved exomes/genomes

STEP 4
Innovative multi-omics approaches for solving the unsolved RD cases

STEP 5
Validate candidate genes in larger cohorts

Implement Solve-RD Models & Mechanisms Network brokerage service for molecular/ functional validation

STEP 6
Communication of (gen)omics test results to patients in an evidence-based manner

Cost effectiveness of –omics technologies in a diagnostics setting

STEP 7
Treatabolome: develop a knowledgebase and tools to enable treatable variants to be flagged up

Create well-characterised, trial-ready cohorts for therapy development and ensure biosample availability

Partners

No.	Beneficiary	City, Country	PIs
1	Eberhard-Karls-Universität Tübingen, Institute of Medical Genetics and Applied Genomics and Center of Neurology	Tübingen	Olaf Riess, Holm Graessner, Stephan Ossowski, Peter Heutink, Rebecca Schüle, Matthis Synofzik
2	Stichting Katholieke Universiteit, Radboud University Medical Centre	Nijmegen	Han Brunner, Hans Scheffer, Nicoline Hoogerbrugge, Alexander Hoischen, Lisenka Vissers, Christian Gilissen
3	University of Leicester	Leicester	Anthony J. Brookes
4	University of Newcastle upon Tyne	Newcastle	Rita Horvath, Teresinha Evangelista
5	Central Manchester University Hospitals NHS Foundation Trust	Manchester	Jill Clayton-Smith, Siddharth Banka
6	Centre Hospitalier Reg Universitaire Dijon	Dijon	Laurence Faivre, Aurore Pélissier, Christine Peyron
7	Centro Nacional de Análisis Genómico, Center for Genomic Regulation	Barcelona	Sergi Beltran, Ivo Gut
8	EURORDIS - Rare Diseases Europe	Paris	Virginie Bros-Facer
9a	Institut National de la Santé et de la Recherche Médicale, Orphanet	Paris	Ana Rath
9b	Institut National de la Santé et de la Recherche Médicale, ICM Brain & Spine Institute	Paris	Giovanni Stevanin, Alexandra Durr
9c	Institut National de la Santé et de la Recherche Médicale, Institute of Myology	Paris	Gisèle Bonne
10	Univerzita Karlova	Prague	Milan Macek
11	European Molecular Biology Laboratory - European Bioinformatics Institute	Hinxton	Helen Parkinson, Thomas Keane, Alexander Senf
12	The Jackson Laboratory	Farmington, Conn.	Peter Robinson
13	King's College London	London	Alison Metcalfe, Christine Patch
14	University College London, Institute of Neurology and Institute of Child Health	London	Mike Hanna, Henry Houlden, Mary Reilly, Francesco Muntoni
15	Universiteit Antwerpen, VIB Center for Molecular Neurology	Antwerpen	Vincent Timmerman, Peter de Jonghe
16	Universita degli Studi della Campania Luigi Vanvitelli	Naples	Vincenzo Nigro
17	Universita degli Studi di Ferrara	Ferrara	Alessandra Ferlini, Rita Selvatici
18	Universitätsklinikum Bonn	Bonn	Stefan Aretz
19	IPATIMUP - Instituto de Patologia Eimunologia Molecular da Universidade do Porto	Porto	Carla Oliveira
20	Academisch Ziekenhuis Groningen	Groningen	Morris Swertz
21	Charité - Universitätsmedizin Berlin	Berlin	Sebastian Köhler

Cohorts

1. Unsolved cases

Definition: Unsolved rare disease cases with an inconclusive exome

Numbers: at least 19,000 cases from ERNs and beyond

Main activities: standardised collation of data and re-analysis with state-of-the art variant calling pipeline

Expected diagnostic efficiency: 3-5% of all cases

2. Specific ERN cohorts

Definition: Disease groups specific cohorts from four core ERNs

Numbers: 2,000 cases WGS to achieve a more complete (non-)coding sequence, structural variants (SVs) etc.; 500 cases long-read WGS; 750 cases deep WES; 800 cases short-read and 80 cases long-read transcriptomics; 360 cases epigenomics (RRBS); 150 cases metabolomics; 140 cases proteomics; 250 cases deep molecular phenotyping (peptide arrays, histology, immune-seq)

Main activities: „beyond the exome" approaches

Expected diagnostic efficiency: 20-30% of all cases. 10% by moving from WES to WGS, 10-20% by adding transcriptomics, and at least 10% estimate by other omics technologies and moving to long read WGS.

3. Ultra-rare Rare Diseases

Definition: Phenotypically most special/remarkable rare diseases patients without an exome

Numbers: 800 cases

Main activities: Phenotype jamborees and exome/genome sequencing

Expected diagnostic efficiency: 50% of all cases; high yield due to exquisite phenotype selection.

4. The Unsolvables

Definition: Highly recognisable clinically defined diseases/syndromes for which no disease gene was identified yet (despite WES/WGS)

Numbers: 120 cases

Main activities: Combination of all available omics tools to 'crack' the "Unsolvables"

Expected diagnostic efficiency: see cohort 2

The Solve-RD project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 779257.

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