RD-Connect: an FP7 success story

D. Badowska[1], L. Wood[1], R. Thompson[1], J. Dawson[1], H. Lochmüller[2,3], I. Gut[3,4] and the RD-Connect Consortium

[1]John Walton Muscular Dystrophy Research Centre, Institute of Genetic Medicine, MRC Centre for Neuromuscular Diseases, Newcastle University, UK; [2]Department of Neuropediatrics and Muscle Disorders, Medical Center–University of Freiburg, Faculty of Medicine, Freiburg, Germany; [3]Centro Nacional de Análisis Genómico (CNAG-CRG), Center for Genomic Regulation, Barcelona Institute of Science and Technology (BIST), Barcelona, Spain; [4]Universitat Pompeu Fabra (UPF), Barcelona, Spain

Summary

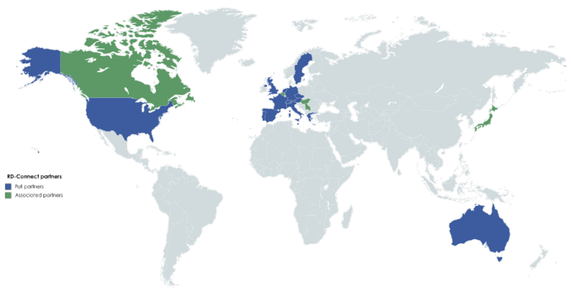
- Although individually uncommon, rare diseases (RDs) collectively affect 6-8% of the population; around 30M people in the EU and 400M worldwide.
- RD research faces specific challenges. Since patients, clinical expertise and research communities are scarce and fragmented, data sharing between researchers is crucial.
- To address this, in 2012 the European Commission awarded a €12M FP7 grant to RD-Connect to create an infrastructure bringing together multiple data types used in RD research into a common resource for researchers and clinicians.
- In six years, RD-Connect developed an integrated platform bringing together analysis tools and different types of data needed in RD research into a common resource for clinicians and researchers worldwide.
- The RD-Connect platform consists of three systems: Genome-Phenome Analysis Platform, Registry & Biobank Finder and Sample Catalogue, which are open to any RD.
- RD-Connect is open for data submissions and already holds thousands of datasets, including linked omics and phenotypic data, biosamples and information about RD patient registries and biobanks. The secure, pseudonymised datasets in RD-Connect are linked at an individual per-patient or per-sample level. Researchers can analyse data, find similar cases and related information such as availability of biomaterials.
- Thanks to the work on data linkage, patient registries and biobanks receive support in making their datasets Findable, Accessible, Interoperable and Reusable (FAIR).
- Successful collaborations with several partner projects, including NeurOmics, EURenOmics and BBMRI-LPC, led to the discovery of over 100 novel disease genes.
- In addition, RD-Connect has developed a number of clinical bioinformatic tools that facilitate data analysis and interpretation and are integrated in the Platform.
- RD-Connect ethical and legal experts developed guidelines for researchers and optimal models for data sharing, while the engagement of patients and patient representatives at every level of the project's work ensured patient-centred approach.
- Collaboration with the European Reference Networks will ensure the impact of RD-Connect on improving RD patients' quality of life.
- RD-Connect is embedded in European and international efforts, including BBMRI, ELIXIR and the International Rare Disease Research Consortium (IRDiRC).
- The project has helped move the field forward by advancing omics research and data sharing and is thus an EU flagship project and an FP7 success story.

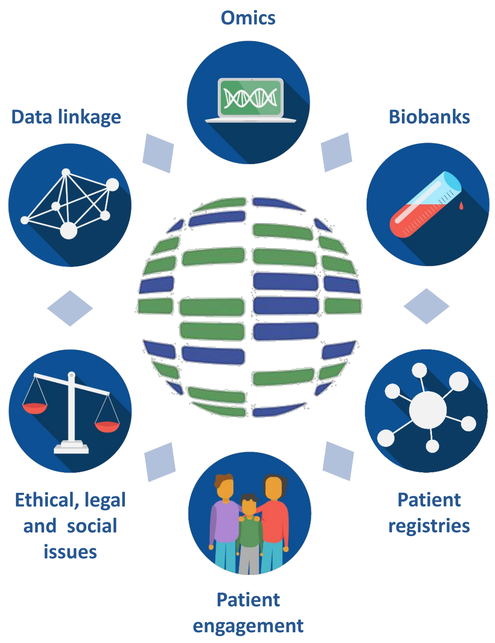
For an overview, watch our explanatory video:

RD-Connect overview

RD-Connect received from the European Commission an **FP7 grant** of €12M over six years (2012-2018) to create a global research infrastructure for rare disease research. RD-Connect is also a flagship project of the International **Rare Diseases Research Consortium (IRDiRC)** implementing IRDiRC policies and guidelines on data sharing. The project has contributed to the IRDiRC goals of 200 new therapies and the means to diagnose most rare diseases by the year 2020, the first of which has already been achieved ahead of time, in early 2017.

RD-Connect unites 29 partners in 15 countries and 20 collaborators in 12 countries. The unique value of the project is that is has built RD community by integrating different stakeholders, such as scientists, clinicians, IT experts, ethicists, lawyers and patients, who otherwise would have limited opportunities to work together.





The RD-Connect infrastructure

RD-Connect has developed a unique platform that links different types of data needed for rare disease research into a common resource : genomics and other omics, phenotypes, patient registries, biobanks and biosamples.

The RD-Connect platform consist of three systems:

- The **Genome-Phenome Analysis Platform** is not only a data repository but also a full-featured genomic analysis interface with a particular focus on diagnosis and gene discovery. It enables researchers and clinicians (even without bioinformatic training!) to easily identify disease causing genes and find matching cases across databases.
- The **Registry & Biobank Finder** is a global directory of RD patient registries and biobanks. It is unique in that for each database it provides regularly updated numbers of registered patients/samples per each disease, including genetic diagnosis, which facilitates preparing clinical trials.
- The **Sample Catalogue** lets researchers browse sample collections and find detailed information about *individual* rare biosamples available in RD biobanks. The tool facilitates the reuse of scarce and valuable biosamples for research.

These three systems are open to any rare disease and accept submissions from users and databases around the world.

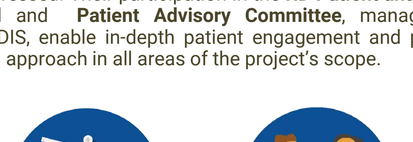
In addition, RD-Connect has developed several **bioinformatic tools** for analysis and interpretation of omics data, e.g. VarAFT, UMD-Predictor, Human Splicing Finder and more.

Through novel mechanisms for **data linkage**, remote resources that hold **Findable, Accessible, Interoperable and Reusable** (FAIR) data can be linked in at a per-patient or per-sample level, enabling researchers to find a cohort or rare sample of interest for further studies.

Ethical, legal & social issues and patient engagement

The genomic era brings new opportunities for people living with rare diseases, particularly those with no genetic diagnosis. It also brings new ethical, legal and social challenges: how do we maximize the benefits and opportunities for new diagnoses and knowledge while minimizing risks relating to sharing genomic data? To ensure protection of patient privacy without compromising research, RD-Connect experts on **Ethical, Legal and Social Issues (ELSI)** provide guidance to researchers and work on the most appropriate models for data sharing, including standardized procedures for informed consent, a charter of principles for data sharing, and work exploring patient attitudes to data sharing. Using the ELSI expertise, RD-Connect has successfully adapted to the requirements of the new European **General Data Protection Regulation (GDPR)**.

Rare disease patients and families are actively engaged in the project to ensure that their needs, concerns and expectations are addressed. Their participation in the **RD Patient and Ethics Council** and **Patient Advisory Committee**, managed by EURORDIS, enable in-depth patient engagement and patient-centred approach in all areas of the project's scope.



Research achievements

RD-Connect has already contributed to advances in RD research and has published over 200 scientific publications and contributed to over 100 gene discoveries.

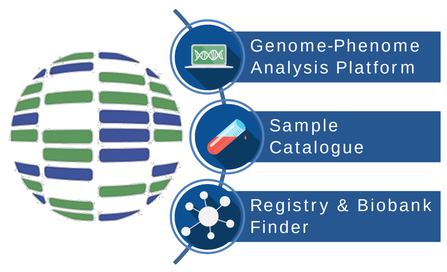
The Genome-Phenome Analysis Platform was used as the primary tool for analysis of 900 exomes that have been sequenced as part of the 17 research projects funded in the **BBMRI-LPC** (www.bbmri-lpc.org) call in 2016.

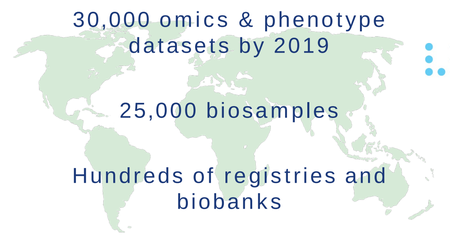
The Genome-Phenome Analysis Platform will be also used by **Solve-RD** (www.solve-rd.eu), a major new Horizon 2020 project to diagnose undiagnosed patients from the European Reference Networks. By the end of 2019, Solve-RD will submit 19,000 exomes to RD-Connect . Thus, at that time, the Platform is expected to hold around **30,000 omics datasets.**

The Registry & Biobank Finder has already recruited hundreds of RD patient registries, and allows users to browse resources covering over 2000 different rare diseases.

The Sample Catalogue enables researchers to find detailed information on individual samples available in RD biobanks. Since its launch in December 2017, it has already received data on **25,000 samples** stored in the pilot biobanks of the EuroBioBank network and will soon increase to encompass the whole network.

These examples show how the reuse of infrastructure developed in one project by its inclusion in new initiatives maximises the value of European funding.





bbmri-lpc
BBMRI – Large Prospective Cohorts

SolveRD

Collaborations

During its development, RD-Connect closely collaborated with two parallel EU-funded research projects *NeurOmics* and *EURenOmics*, which applied omics technologies to study rare neuromuscular & neurodegenerative and rare kidney diseases. Thanks to this fruitful collaboration, RD-Connect received submissions of omics data, while the feedback from end-users allowed the RD-Connect tools to be optimised for the needs of RD researchers. RD-Connect supported both projects in gene discovery and data linkage, which facilitated diagnosis and therapy development.

Similarly, the collaboration with *EuroBioBank*, the European network of biobanks which became the first *de facto* biobank of RD-Connect, was fundamental for the development of the Sample Catalogue.

RD-Connect, along with *NeurOmics* and *EURenOmics*, are embedded in European collaborative projects such as IRDiRC and research infrastructures such as BBMRI and ELIXIR.

RD-Connect has also initiated collaborations with the **European Reference Networks (ERNs)**, which connect RD experts and healthcare providers across the EU. RD-Connect is supporting the ERNs in their research goals and in creating FAIR patient registries. This collaboration will greatly increase the project's impact on improving of the quality of life of RD patients.

NeurOmics
BBMRI-ERIC®
European Reference Networks
EURenOmics
elixir
EuroBioBank

International recognition

The value of RD-Connect has been recognised by the international RD community. The European Commission's Directorate-General for Research has included RD-Connect among its Research and Innovation success stories and promoted it using its dissemination channels, publications and interviews in several EU journals.

To fundamental role of RD-Connect in RD research has been also acknowledged by IRDiRC, which has awarded the label "**IRDiRC recognized resource**" to three RD-Connect outputs: *The International Charter of principles for sharing bio-specimens and data* (2015), *Guidelines for the informed consent process in international Rare Disease Research* (2016) and *Genome-Phenome Analysis Platform* (2018). IRDiRC has also endorsed *The FAIR Guiding Principles for scientific data management and stewardship*. (2017), which have been developed with significant involvement of RD-Connect partners.

The role of data sharing has been reflected in two **major calls for rare disease research** in 2018, announced by E-Rare (www.erare.eu) and by the German Federal Ministry of Education and Research. Both calls mandate the use of infrastructure like RD-Connect for omics sharing and analysis.

The success of RD-Connect in advancing RD research makes it a flagship project of the European Commission.

European Commission
IRDiRC RECOGNIZED RESOURCES
E-Rare
Bundesministerium für Bildung und Forschung

References

- *Lochmüller H & Badowska D, el al. RD-Connect, NeurOmics and EURenOmics: Collaborative European Initiative for Rare Diseases. Eur J Hum Genet 2018*
- *Thompson R, et al. RD-Connect: an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. J Gen Intern Med 2014*
- *Gainotti S, et al. The RD-Connect Registry & Biobank Finder: a tool for sharing and integrating aggregated data and metadata among rare disease researchers data sharing and data integration in rare disease research. Eur J Hum Genet. 2018*
- *Gainotti S, et al. Improving the informed consent process in international collaborative rare disease research: effective consent for effective research. Eur J Hum Genet. 2016*
- *Mascalzoni D, et al. International Charter of principles for sharing bio-specimens and data. Eur J Hum Genet. 2014*

rd-connect.eu

IRDiRC INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

The John Walton MUSCULAR DYSTROPHY RESEARCH CENTRE

The Newcastle upon Tyne Hospitals NHS Foundation Trust

Newcastle University

cnag centre nacional d'anàlisi genòmica centro nacional de análisis genómico

RD Connect

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 2012-305444