

The RD Connect Platform

Steve Laurie
Variant Effect Predictor
Training Course
Prague, 7th November 2017

cnag

centre nacional d'anàlisi genòmica
centro nacional de análisis genómico

 **CRG[®]**
Centre
for Genomic
Regulation





The RD-Connect Platform

2

- 1) What is RD-Connect
- 2) What **you** can do with the RD-Connect Genome-Phenome Analysis Platform (GPAP)
- 3) Case study – the BBMRI-LPC WES call



RD-Connect: Infrastructure for Rare Disease Research

3

6-year project funded by EU 7th Framework Programme
**An integrated platform connecting data, clinical
information, registries, and biobanks for rare disease research**

- Creating a central system for **reprocessing, storing, analysing** and **sharing** of **-omics** data, including the integration of **phenotypic** and **biosample** data
- Contributing to **International Rare Diseases Research Consortium (IRDiRC)** objectives of delivering 200 new therapies, and means to diagnose most rare diseases of genetic etiology by 2020



What are rare/orphan diseases?

4



**RARE
DISEASES**



**7% OF THE
POPULATION
ARE AFFECTED BY
RARE DISEASES**

THE EU CLASSES A
DISEASE AS 'RARE' WHEN
**LESS THAN
1 IN 2000 SUFFER**



**OVER 7000
DISEASES**

**80% GENETIC IN
ORIGIN.**

**OFTEN CHRONIC
AND LIFE-
THREATENING**



JUGGLING CARE AND DAILY LIFE: THE BALANCING ACT OF THE RARE DISEASE COMMUNITY

**Huge social impact
on patients and
their carers**

Through its survey initiative Rare Barometer Voices, EURORDIS-Rare Diseases Europe carried out the first European-wide survey on the impact of rare diseases on everyday life. The survey covered issues including coordination of care, mental health, employment and economic impact. See the full survey report at eurordis.org/voices#studies



30 million
people are living with a rare disease in Europe
and 300 million worldwide



No cure for the vast majority of diseases and
few treatments available

Rare diseases seriously impact everyday life

7 in 10 patients
& carers

reduced or stopped
professional activity due to
their or their family
member's rare disease.

2/3 of carers

spend more than 2 hours a
day on disease-related tasks.

8 in 10 patients
& carers

have difficulties completing
daily tasks (household
chores, preparing meals,
shopping etc.)

3 times
more people

living with a rare disease and
carers report being unhappy
and depressed than the general
population*

* Rare Barometer Voices sample compared to International Social Survey Programme, 2011



EURORDIS #INITIATIVE

Rare Barometer Voices is a EURORDIS-Rare Diseases Europe online survey initiative. It brings together over 6,000 patients, carers and family members to make the voice of the rare disease community stronger. Results are shared with policy decision makers to bring about change for people living with a rare disease.



Thank you to all Rare Barometer
Voices participants and partners!

www.eurordis.org/content/contribute-rare-barometer-programme

3,071
people responded
to the survey.

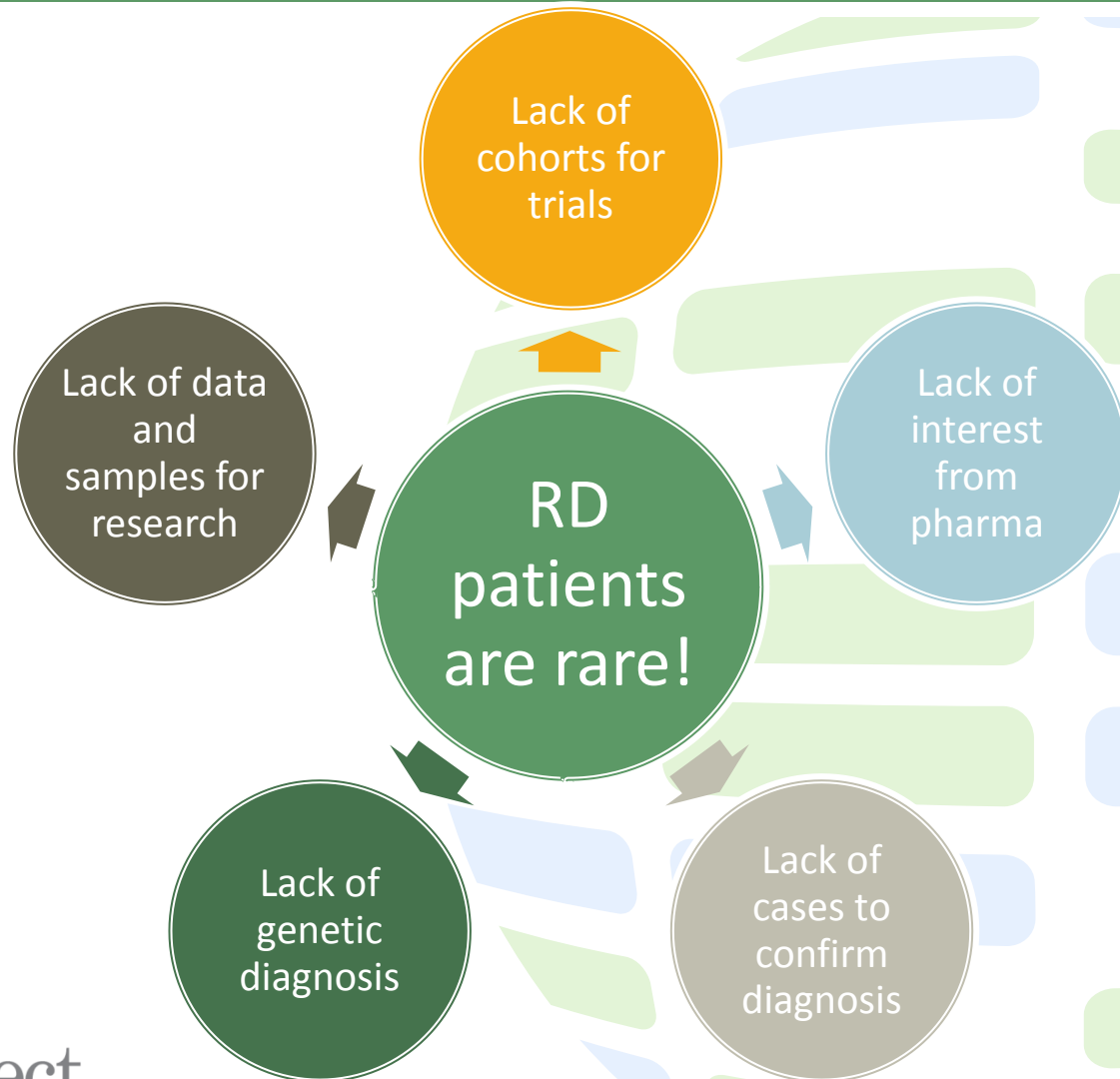
The survey was conducted in
23 languages
42 countries

For more information visit
eurordis.org/voices or email
rare.barometer@eurordis.org



Bottlenecks in RD research

6





Many bottlenecks are cross-cutting

7

... across diseases and across research domains

- A lot of them come down to **data**
- Not just scarcity of data, but lack of options to reuse the data that does exist
 - **Privacy protection issues**, particularly across borders
 - **Lack of infrastructure** for data sharing
 - **Lack of standards** and interoperability
 - **Reluctance to share** unpublished data
 - **Lack of capacity to analyse** large amounts of data
 - **Challenges of linking different datasets** in different places

Infrastructure for data sharing in rare disease research

Flagship IRDiRC project implementing IRDiRC policies and guidelines on data sharing

EU 7th Framework Programme, 12M EUR, 6 years

Genomic analysis and gene discovery

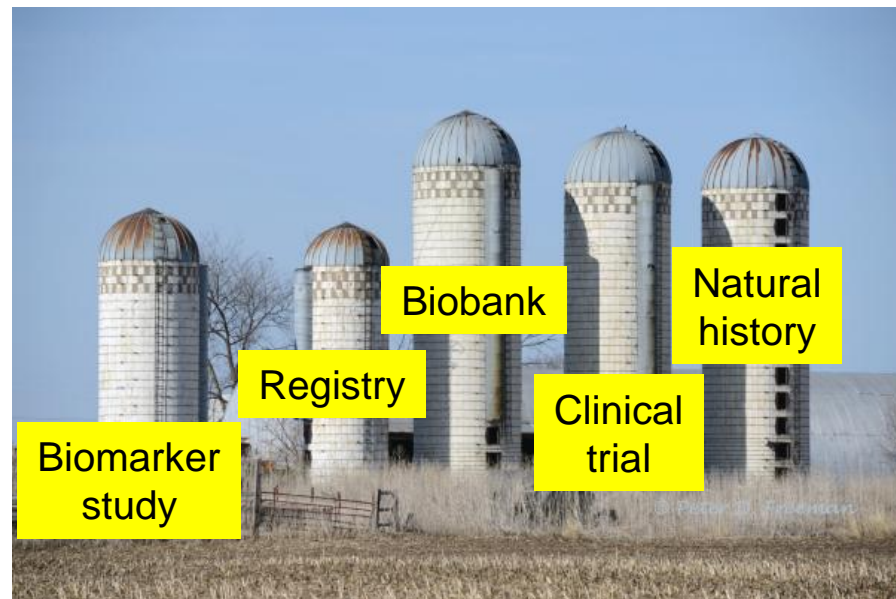
Standardized phenotypic data collection

Searchable catalogue of biosamples

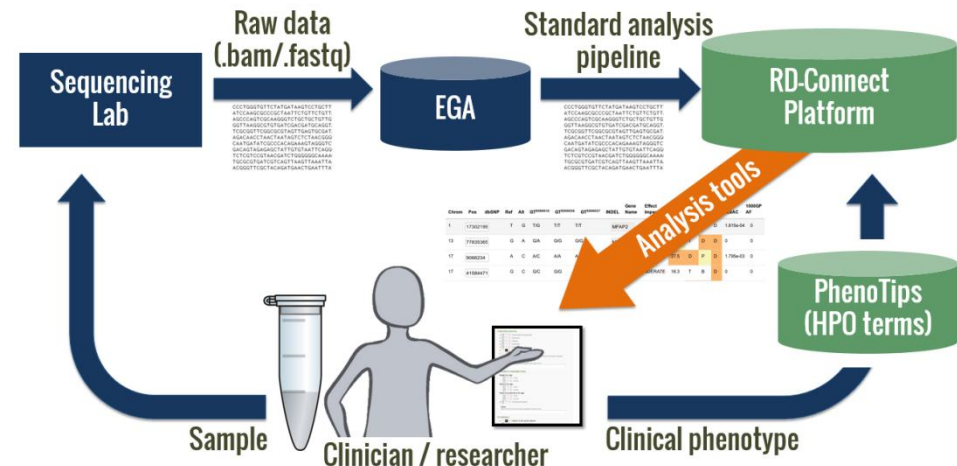
Data linkage across resources

Overcoming Silos

Data sharing for research and better data analysis



Omics data, clinical data and biosamples from an individual with RD



Disease-causing variants can be identified using the [Genome-Phenome Analysis Platform](#)

Samples findable in the [Biosample Catalogue](#)

Registry data findable in the [Registry and Biobank Finder](#)



RD-Connect Platform

9



Home

Genome-Phenome Analysis
Platform

PhenoTips

Registry & Biobank Finder

Biosample

An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research

Welcome to the central platform for access to data submitted by RD-Connect's partner projects. The online Genome-Phenome Analysis Platform is now open for submissions from all users. Our automated registration system will come online shortly, but if you would like to access the interface now please email platform@rd-connect.eu and we will contact you to request the information we need to set you up on the system.

Get started today



platform.rd-connect.eu



Linking up rare disease research across the world

Catalogue

Search

Help Request

Search

duchenne

Search

Search for: duchenne

Search returned 113 hits (Registries:34 /Biobanks:8)



D
M
D

[Australian National Duchenne Muscular Dystrophy Registry](#)

[Caroline Graham](#)

<https://nmdregistry.com.au/dmd/https://nmdregistry.com.au/index.html>

Duchenne muscular dystrophy: Number of Patients, Donors 482

Diseases

DiseaseName: **Duchenne** muscular dystrophy

DiseasesSynonym: Severe dystrophinopathy, **Duchenne** type, DMD

Organization OrganizationName: Australian National **Duchenne** Muscular Dystrophy Registry

[Congenital Muscular Disease International Registry](#)

[Rachel Alvarez](#)



ID # 77350

Date of Inclusion: 01/04/2015

Last Activities: 21/04/2017



Galliera Genetic Bank

The GGB is located at Genetics Laboratory – of Galliera Hospital in Genoa and collects samples from patients affected by chromosomal disorders several genetic diseases since 1983. To date the biobank

[Overview](#)
[17][Diseases](#)
[132][Documents](#)
[0][Website Link](#)

Host institution

Laboratory of Human Genetics -
E.O. Ospedali Galliera
Via Alessandro Volta, 6
16128 Genova
Italy

Tel.0039010563-4383

Fax.0039010563-4381

General Information

Acronym: **GGB**Type of Host Institution: **Hospital**

Source of funding:

Target population:

Year of establishment: **1983**

Personnel

Main contact

Chiara Baldo
Curator

chiara.baldo@galliera.it



Sample-level catalogue (under development)

12

The RD-Connect Sample Catalogue contains information on available samples across participating biobanks

The screenshot displays the RD-Connect Sample Catalogue interface. The top navigation bar includes links for Sample Catalogue, EuroBioBank, Data Integration, Admin, Feedback, and Account, along with a Sign out button. The main header shows 'Sample Catalogue' and 'Sample Information'. A search bar is present with a search icon and a 'Delete' button. Below the search bar, there are tabs for Data, Aggregates, Charts, and Annotators. The left sidebar contains 'Data item filters' and 'Data item selection' sections. The 'Data item selection' section lists various data items with checkboxes, including Sample ID, Disease, MIABIS Material Type, Material Type, Anatomical Site, Sex, Diagnosis Type, Genotype data, Age at Sampling, Age at Death, Age at Diagnosis, Age at Remission, Affected, Family members available, Related samples available, Registry data available, Hosting Biobank, Hosting Registry, and Participant ID. The main content area displays a table of sample data with columns for Sample ID, Disease, MIABIS Material Type, Material Type, Anatomical Site, Sex, Diagnosis Type, and Genotype data. The table lists 20 rows of sample data. At the bottom, there is a 'Rows per page' dropdown set to 20, a pagination bar showing 'Previous', '1', '2', '3', '4', '5', '6', '...', '368', and 'Next', and a note '7352 items found'.

Sample ID	Disease	MIABIS Material Type	Material Type	Anatomical Site	Sex	Diagnosis Type	Genotype data
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaae	Ring chromosome 14	Blood	Leukocyte	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaae	Ring chromosome 14	Immortalized Cell Lines	Lymphoblast	Blood	Male	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaai	Ring chromosome 14	Blood	Leukocyte	Blood	Male	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaam	Ring chromosome 14	DNA	DNA	Blood	Male	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaae	Ring chromosome 14	DNA	DNA	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaai	Ring chromosome 14	Blood	Leukocyte	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaam	Ring chromosome 14	Immortalized Cell Lines	Lymphoblast	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaae	Ring chromosome 14	DNA	DNA	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaai	Ring chromosome 14	Blood	Leukocyte	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaam	Ring chromosome 14	DNA	DNA	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaam	Ring chromosome 14	Immortalized Cell Lines	Lymphoblast	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaai	Ring chromosome 14	Immortalized Cell Lines	Lymphoblast	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaae	Ring chromosome 14	Immortalized Cell Lines	Lymphoblast	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaai	Ring chromosome 14	DNA	DNA	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaam	Ring chromosome 14	Immortalized Cell Lines	Lymphoblast	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaai	Ring chromosome 14	Other	Fibroblast	Skin	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaae	Ring chromosome 14	DNA	DNA	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaai	Ring chromosome 14	DNA	DNA	Blood	Female	Molecular,Cytogenetics	Yes
urn:rdconnect.tngb:aaaacwysgmweb6qwhz3mx2aaam	Ring chromosome 14	Immortalized Cell Lines	Lymphoblast	Blood	Female	Molecular,Cytogenetics	Yes



RD-Connect: Ethical and Legal Issues

13

- Database registered in the Agencia Española de Protección de Datos
- To submit and/or to access donor data, a **Code of Practice** and **Adherence Agreement** must be signed
- Documents were approved by Comité Ètic d'Investigació Clínica del Parc de Salut Mar in 2015
- **User-activity is logged**



RD-Connect: Helping you share your data

14

RD-Connect enables:

- Full data sharing and analysis within RD-Connect for **registered users**
- Partial data sharing outside RD-Connect (in accordance with ethical and legal limitations)
- A core requirement of having data incorporated into RD-Connect is that that **corresponding phenotypic descriptions for all donor samples must be entered** into the RD-Connect PhenoTips instance
- If you **share your data**, you are more likely to solve your cases e.g. through internal and external **matchmaking (MME)**



RD-Connect: Helping you share **your patients' data** (with consent)

15

RD-Connect enables:

- Full data sharing and analysis within RD-Connect for **registered users**
- Partial data sharing outside RD-Connect (in accordance with ethical and legal limitations)
- A core requirement of having data incorporated into RD-Connect is that that **corresponding phenotypic descriptions for all donor samples must be entered** into the RD-Connect PhenoTips instance
- If you **share your patients' data**, you are more likely to solve your cases e.g. through internal and external **matchmaking (MME)**



Data Sharing: GA4GH Beacon








16

GRCh37 ▾ 13 : 32954208 A>T Search

Response	All None
<input checked="" type="checkbox"/> Found	8
<input checked="" type="checkbox"/> Not Found	43
<input type="checkbox"/> Error	8

Organization All None

- ☐ AMPLab, University of C...
- ☐ BGI
- ☐ BioReference Laboratories
- ☒ Broad Institute
- ☐ Centre for Genomic Regu...
- ☒ CNAG
- ☐ Curoverse
- ☐ DNASTack
- ☒ EMBL European Bioinfor...
- ☐ Global Alliance for Geno...
- ☐ Google
- ☒ Institute for Systems Biol...
- ☒ Mike Lin
- ☒ National Center for Biote...

	EBI - 1000 Genomes Project, ... EMBL European Bioinformatics Institute	Not Found
	ExAC Broad Institute	Not Found
	ICGC - Cancer Projects Ontario Institute for Cancer Research	Not Found
	Kaviar Institute for Systems Biology	Found
	NHLBI Exome Sequence Proj... National Center for Biotechnology Information	Not Found
	RD-Connect CNAG	Not Found
		Not Found

Question:

Does any sample in
your database have
variant V?

Answer:

Yes / No



Data Sharing: MatchMaker Exchange (IRDIRC, GA4GH)

17



Question:

Do you have a patient with a *similar phenotype* and *similar variants* to mine in your database?

Answer:

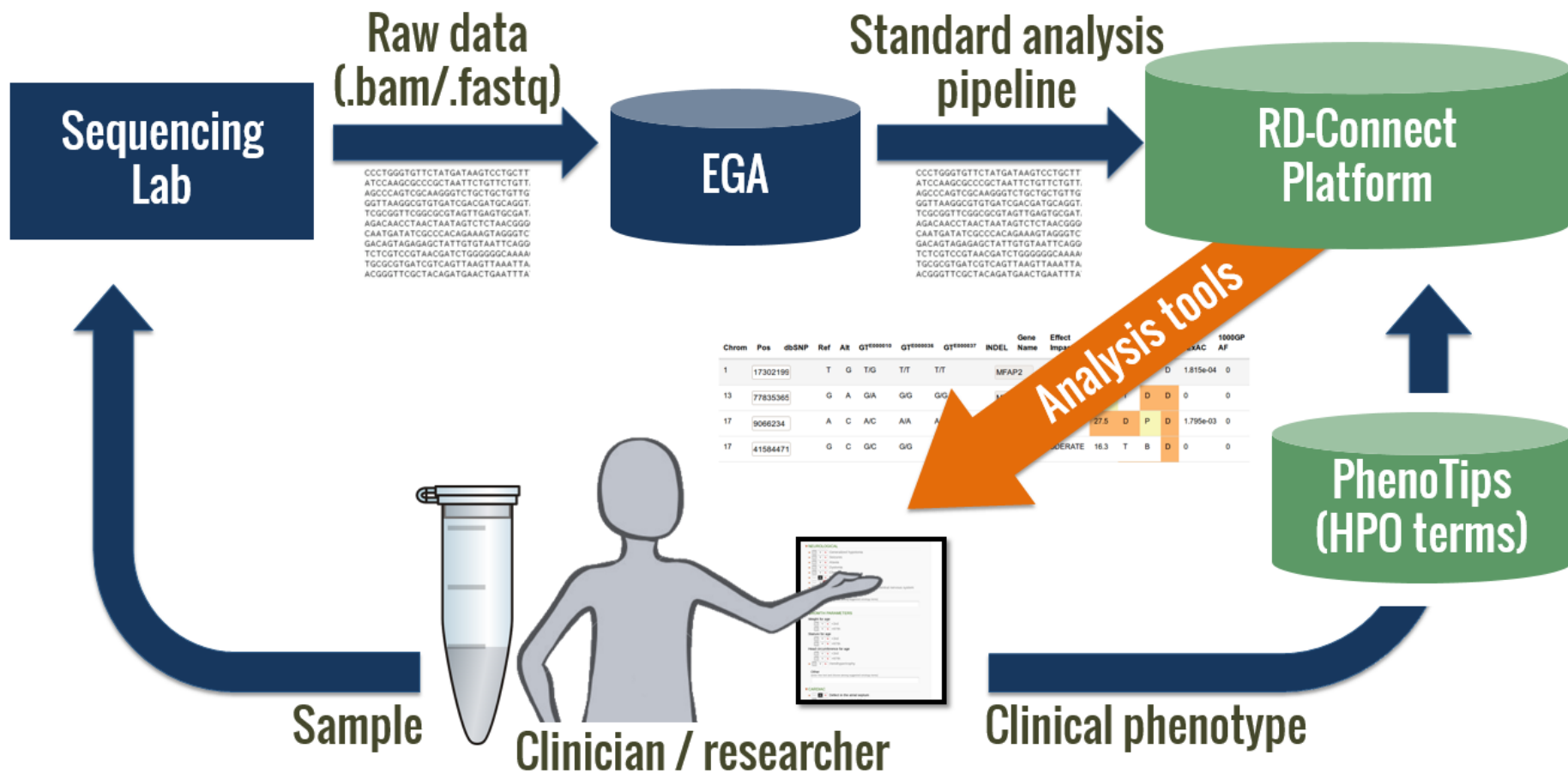
No / Yes – here are some of the details of some *similar individuals*

Philippakis, A.A. et al. (2015)



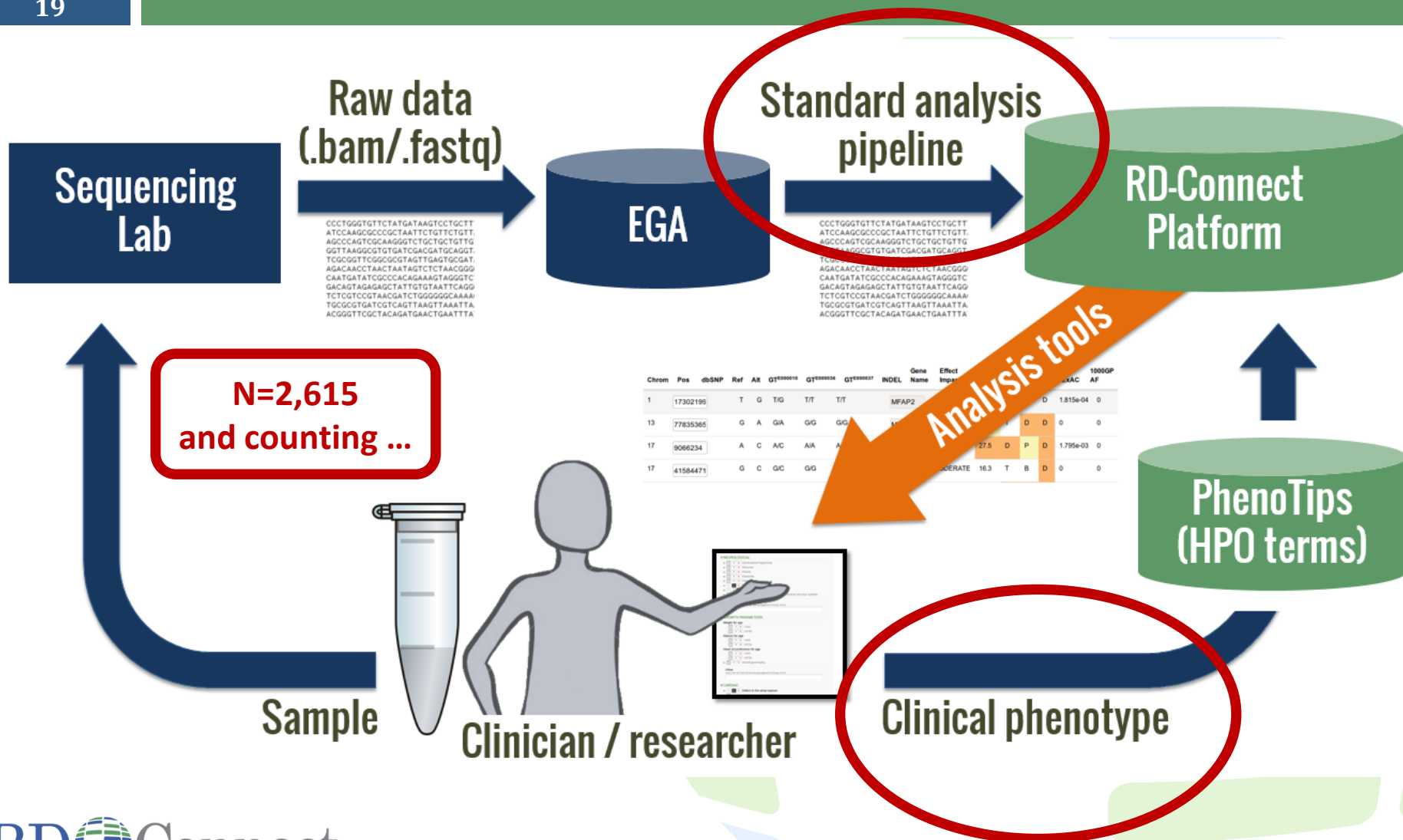
Genome-phenome data flow into RD-Connect

18



Genome-phenome data flow into RD-Connect

19





RD-Connect PhenoTips Instance

20

▼ NEUROLOGICAL

- ☐ NA ☒ Y ☐ N Generalized hypotonia
- ☐ NA ☒ Y ☐ N Seizures
- ☐ NA ☒ Y ☐ N Ataxia
- ☐ NA ☒ Y ☐ N Dystonia
- ☐ NA ☒ Y ☐ N Chorea
- ☐ NA ☒ Y ☐ N Spasticity
- ☐ NA ☒ Y ☒ N **Spinal dysraphism**
- ☐ NA ☒ Y ☐ N Morphological abnormality of the central nervous system

Other
(enter free text and choose among suggested ontology terms)

▼ GROWTH PARAMETERS

Weight for age

☐ NA ☒ Y ☐ N <3rd

☐ NA ☒ Y ☐ N >97th

Stature for age

☐ NA ☒ Y ☐ N <3rd

☐ NA ☒ Y ☐ N >97th

Head circumference for age

☐ NA ☒ Y ☐ N <3rd

☐ NA ☒ Y ☐ N >97th

☐ NA ☒ Y ☐ N Hemihypertrophy

Other
(enter free text and choose among suggested ontology terms)

▼ CARDIAC

☐ NA ☒ Y ☐ N Defect in the atrial septum

Onset

- ☒ Congenital onset
 - ☐ Embryonal onset
 - ☐ Fetal onset
 - ☐ Neonatal onset
 - ☐ Infantile onset
- ☐ Juvenile onset
- ☐ Adult onset
 - ☐ Young adult onset
 - ☐ Middle age onset
 - ☐ Late onset

Pace of progression:

- ☒ Unknown
- ☐ Nonprogressive disorder
- ☐ Slow progression
- ☐ Progressive disorder
- ☐ Rapidly progressive
- ☐ Variable progression rate

Comments:
No complications

Image / photo (optional):

Medical report (optional):

Deep phenotyping in
PhenoTips (Brudno *et al.*)
achieved using the **Human
Phenotype Ontology** (HPO
– Robinson, Köhler *et al.*)

Diseases classified using
the **Orphanet Rare
Disease Ontology** and
OMIM identifiers

Information from PhenoTips can be sent
directly to other tools within the platform
(e.g. Exomiser, MME)



RD-Connect PhenoTips Instance

21

PHENOTIPS

» DATA » P0000700

NEW PATIENT RECORD

P0000700

Reported by **Irina Zaharleva** on 2014/06/16 10:13 · Last modified by **Rachel Thompson** on 2016/07/29 06:40

I confirm that patient consent has been obtained which allows next generation sequencing of the sample to which the data refers

I confirm that patient consent has been obtained which allows the sharing of this anonymised clinical information with international collaborators and researchers including those from commercial partners

Patient information

Identifier: DNC0010

Sex: Female

Clinical status

FAMILY STUDY

This patient is the Child

Of patient with identifier [DNC0040](#)

This patient is the Child

Of patient with identifier [DNC0041](#)

Global mode of inheritance:

Sporadic

NO Consanguinity

Global pace of progression

Progressive

Global age of onset:

Congenital onset

Clinical symptoms and physical findings



RD-Connect PhenoTips Instance

22

Clinical symptoms and physical findings

COGNITIVE DYSFUNCTION

NO Intellectual disability

⚠ Normal cognitive development

MUSCLE BULK

Distal arthrogryposis

Arthrogryposis multiplex congenita

SKELETAL DEFORMITIES

Congenital hip dislocation

WEAKNESS

Face

Neck

MOTOR ABILITY

Inability to walk

⚠ can crawl and stand with KAFOs at 4 yrs

OTHER SIGNS

Recurrent lower respiratory tract infections

Muscular hypotonia

INVESTIGATIONS

Muscle biopsy

⚠ Suggestive of CMY

Diagnosis

OMIM disorder:

[117000] #117000



RD-Connect PhenoTips Instance

23

P0003641

Reported by demo user on 2016/10/24 04:57 · Last modified on 2016/10/24 04:57

✓ Save ▾ ⌛ Cancel

☐ I confirm that patient consent has been obtained which allows next generation sequencing of the sample to which the data refers

☐ I confirm that patient consent has been obtained which allows the sharing of this anonymised clinical information with international collaborators and researchers including those from commercial partners

This case is owned by **you** and is **private**. It is shared with

[Patient information](#)

[Family history and pedigree](#)

[Prenatal and perinatal history](#)

[Medical history](#)

[Measurements](#)

[Ataxia tests](#)

[Genotype information](#)

[Onset data](#)

[Unified Huntington's Disease Rating Scale \(UHDRS\) and Total Functional Capacity \(TFC\) data](#)

[Clinical symptoms and physical findings](#)

[Diagnosis](#)

[Case resolution](#)

[Medication](#)



RD-Connect PhenoTips Instance

24

FAMILY STUDY

✓ Save ▼ ⌵ Cancel ☰ J

+ NEW ENTRY ?

Global mode of inheritance:

- ☐ Sporadic ⓘ
- ▼ ☐ Autosomal dominant inheritance ⓘ
 - ▼ ☐ Sex-limited autosomal dominant ⓘ
 - ☐ Male-limited autosomal dominant ⓘ
 - ☐ Autosomal dominant somatic cell mutation ⓘ
 - ☐ Autosomal dominant contiguous gene syndrome ⓘ
 - ☐ Autosomal recessive inheritance ⓘ

- ▼ ☐ Gonosomal inheritance ⓘ
 - ▼ ☐ X-linked inheritance ⓘ
 - ☐ X-linked dominant inheritance ⓘ
 - ☐ X-linked recessive inheritance ⓘ
 - ☐ Y-linked inheritance ⓘ
- ▼ ☐ Multifactorial inheritance ⓘ
 - ☐ Digenic inheritance ⓘ
 - ☐ Oligogenic inheritance ⓘ
 - ☐ Polygenic inheritance ⓘ
 - ☐ Mitochondrial inheritance ⓘ

NA Y N Consanguinity

Global pace of progression

- ☒ Unknown
- ☐ Nonprogressive ⓘ
- ☐ Slow progression ⓘ

- ☐ Progressive ⓘ
- ☐ Rapidly progressive ⓘ
- ☐ Variable progression rate ⓘ

Global age of onset: ?

- ☒ Unknown
- ☐ Congenital onset ⓘ
- ☐ Neonatal onset ⓘ
- ☐ Infantile onset ⓘ
- ☐ Childhood onset ⓘ

- ☐ Juvenile onset ⓘ
- ▼ ☐ Adult onset ⓘ
 - ☐ Young adult onset ⓘ
 - ☐ Middle age onset ⓘ
 - ☐ Late onset ⓘ

[Family history and pedigree](#)

[Prenatal and perinatal history](#)

[Medical history](#)



RD-Connect PhenoTips Instance

25

Clinical symptoms and physical findings

✓ Save ▼

☐ This patient is clinically normal

Or select observed phenotypes: ?



Quick phenotype search:

Enter keywords and choose from the suggested ontology terms

BROWSE CATEGORIES

⊕ EXPAND ALL

⊞ COLLAPSE ALL

▶ OCULAR SIGNS

▶ BULBAR SIGNS

▶ COGNITIVE DYSFUNCTION

▼ MUSCLE BULK

Muscle atrophy

- | | | | | | | | |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|-------------------------------|--------------------------------------|
| <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Proximal upper limb atrophy ⓘ | |
| ▶ | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Neck muscle atrophy ⓘ |
| | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Proximal lower limb muscle atrophy ⓘ |
| | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Paraspinal muscle atrophy ⓘ |
| ▼ | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Distal upper limb muscle atrophy ⓘ |
| ▶ | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Hand muscle atrophy ⓘ |
| | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Scapular muscle atrophy ⓘ |
| ▼ | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Distal lower limb muscle atrophy ⓘ |
| | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Tibialis atrophy ⓘ |
| | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Facial muscle atrophy ⓘ |

Muscle Hypertrophy

- | | | | | | | | |
|---|--------------------------|----|--------------------------|---|--------------------------|---|--|
| ▶ | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Proximal upper limb muscle hypertrophy ⓘ |
| | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Neck muscle hypertrophy ⓘ |
| ▶ | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Proximal lower limb muscle hypertrophy ⓘ |
| | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Paraspinal muscle hypertrophy ⓘ |
| ▶ | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Distal upper limb muscle hypertrophy ⓘ |
| | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Scapular muscle hypertrophy ⓘ |
| ▶ | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Distal lower muscle hypertrophy ⓘ |
| | <input type="checkbox"/> | NA | <input type="checkbox"/> | Y | <input type="checkbox"/> | N | Facial muscle hypertrophy ⓘ |

Other

Enter free text and choose among suggested ontology terms

CURRENT SELECTION

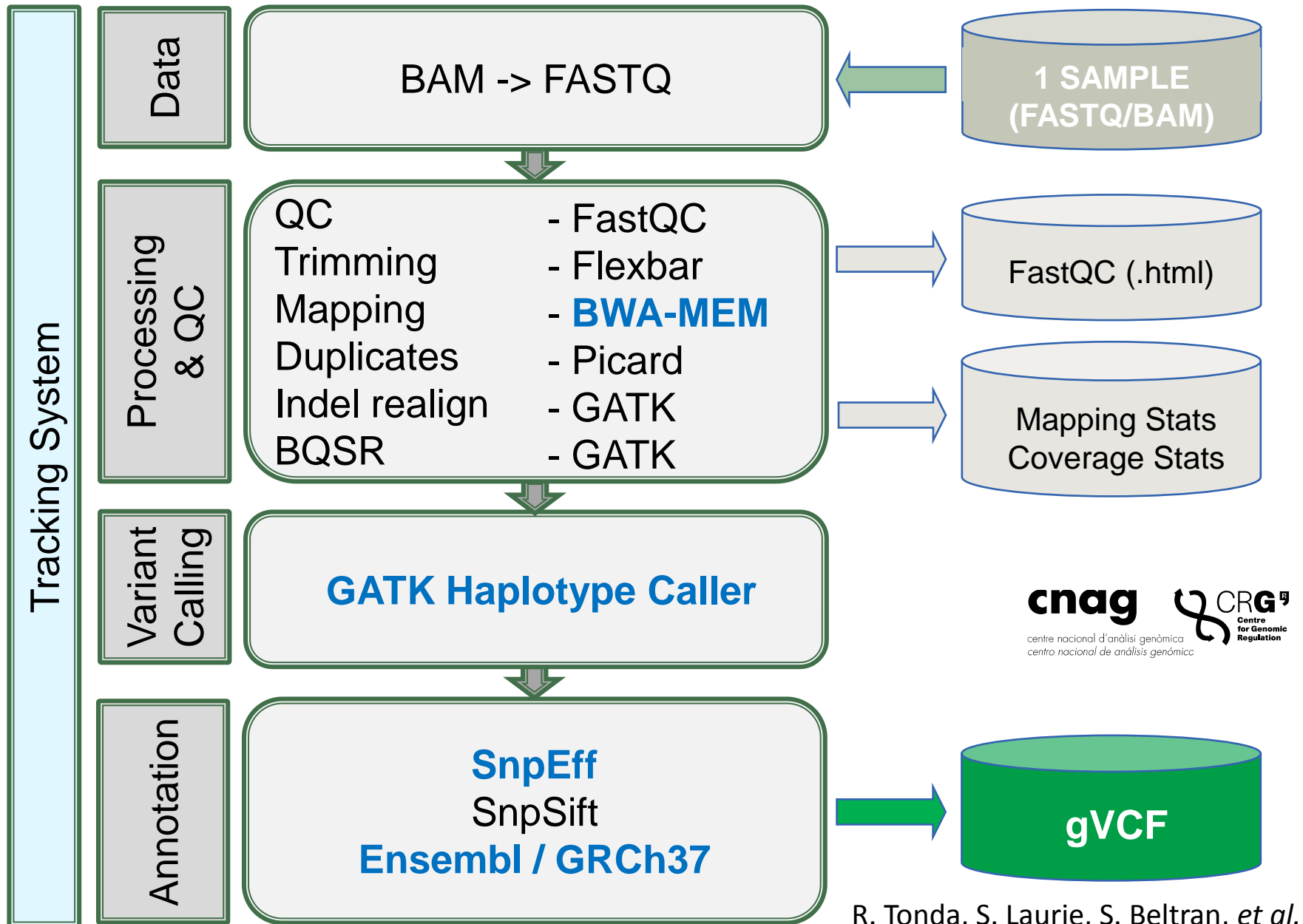
How informative is your phenotypic description: ★★★★★

MUSCLE BULK

Distal upper limb amyotrophy

Hand muscle atrophy

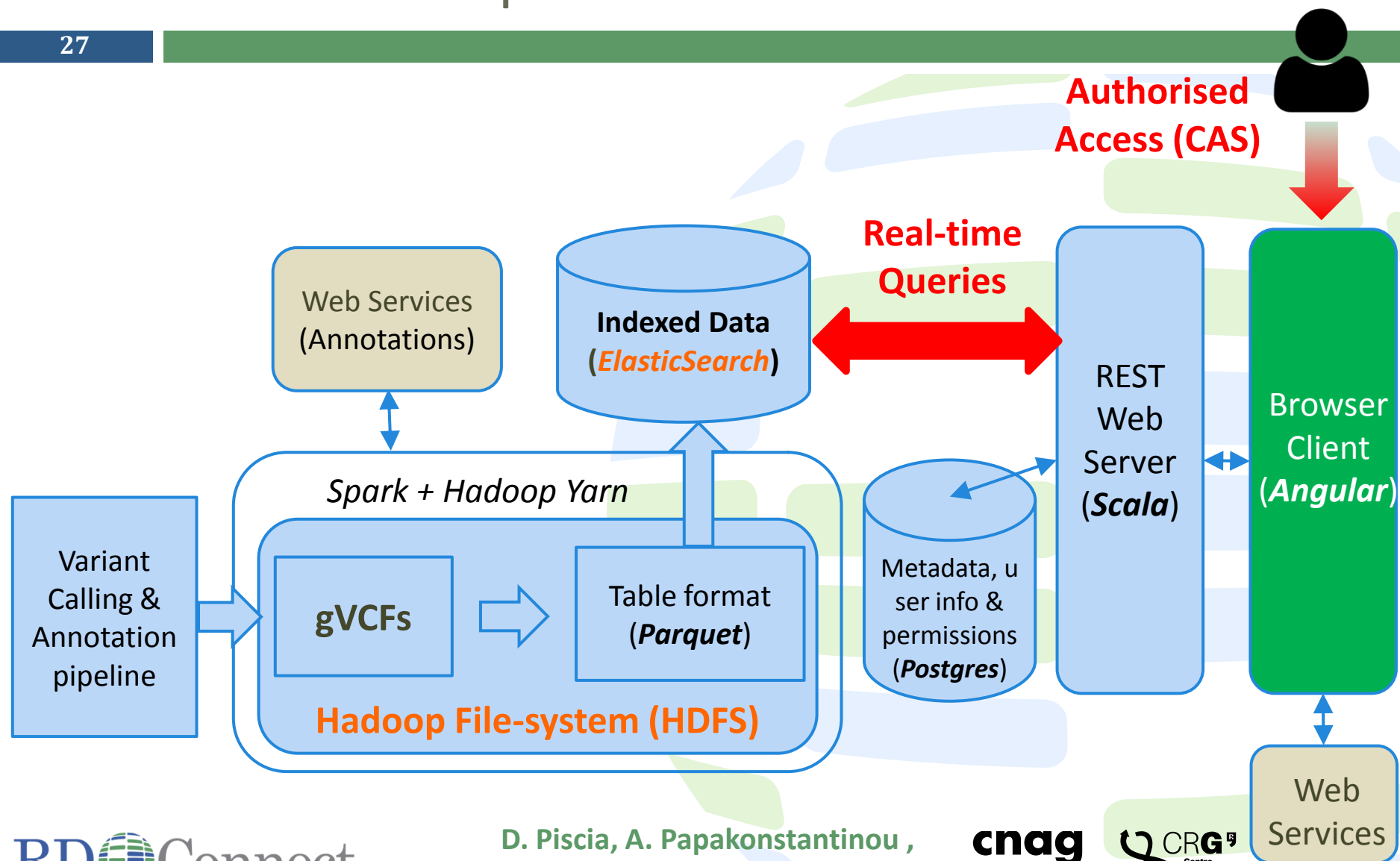
RD-Connect Variant Calling Pipeline





RD-Connect: Genomics platform architecture

27





RD-Connect GPAP Interface

28



GENOMICS

ABOUT

WELCOME S.BELTRAN

{PLATFORM V0.13.0, DATASET 20170426 }

FAQ

LOGOUT

Filters ▼

PRESET FILTERS

RESET

SHARE

▶ RUN QUERY

Variant Type: coding high moderate Population: exac SNV->MT: A D SNV->SIFT: D SNV->PP2: D P

Samples	Functional	Predictive	Population	Diseasecard	Candidate	Links	ALFA				
Gene Name	Transcript ID	Effect Impact	Consequence	Feature Type	HGVS coding	Amino Acid change	Amino Acid length	Genotype Number	Exon Rank	CDS Position	Transcript BioType
MFAP2	ENST00000375531	MODERATE	missense_variant	transcript	c.313A>C	p.Thr105Pro	183	1	7/9	313/552	protein_coding
MFAP2	ENST00000375534	MODERATE	missense_variant	transcript	c.310A>C	p.Thr104Pro	182	1	6/8	310/549	protein_coding
MFAP2	ENST00000438541	MODERATE	missense_variant	transcript	c.310A>C	p.Thr104Pro	182	1	7/9	310/549	protein_coding

Variants (11)

Exomiser

First

Previous

1

Next

Last

EXPORT ALL

Chr	Pos	dbSNP	Ref	Alt	Candidate	GT ^{E000010}	GT ^{E000036}	GT ^{E000037}	INDEL	Gene Name	Effect Impact	ClinVar	CADD	SIFT	PP2	MT	ExAC	1000GP AF
1	17302199	.	T	G	0 ADD	T/G	T/T	T/T		MFAP2	MODERATE		26.9	D	D	D	NA	0
11	93535027	.	C	A	0 ADD	C/A	C/C	C/C		MED17	MODERATE		34	D	D	D	NA	0
13	77835365	.	G	A	0 ADD	G/A	G/G	G/G		MYCBP2	MODERATE		25.6	T	D	D	NA	0
13	110437802	.	A	C	0 ADD	A/C	A/A	A/A		IRS2	MODERATE		24.6	D	D	D	NA	0
13	113210444	.	G	T	0 ADD	G/T	G/G	G/G		TUBGCP3	MODERATE		< 20	T	B	D	NA	0
17	9066234	.	A	C	0 ADD	A/C	A/A	A/A		NTN1	MODERATE		26.7	D	P	D	NA	0



GPAP Interface – Filters

29

Filters ^

PRESET FILTERS

RESET

SHARE

▶ RUN QUERY

Sample Selection ?



Select individual Samples ☐ or search across all ☐ ? (accessible: 1993, own: 0, shared: 814, visible to all: 1331)

Variant Type ?



Population ?



SNV Effect Prediction?



Genes, Disorders and Phenotypes



Position Specific filters and Runs Of Homozygosity





GPAP Filters – Variant Type

30

Variant Type ?

Variant Class

- ☐ High
- ☐ Moderate
- ☐ Low
- ☐ Modifier

ClinVar Classification

- ☐ Pathogenic-(5)
- ☐ Likely pathogenic-(4)
- ☐ Any

Variant Type

- ☐ SNV
- ☐ INDEL

Transcript Biotype

- ☐ Protein_coding
- ☐ RNA
- ☐ Other



GPAP Filters – Runs Of Homozygosity

31

Position Specific filters and Runs Of Homozygosity

Chr

	▼
Start	▼
End	▼

Upload BED file

No file selected.

Minimum run of homozygosity length

- ☐ 0.5MB
☐ 1.0MB
☐ 2.0MB

Upload coordinate file

No file selected.



GPAP Filters – Genes & Phenotypes

32

Genes, Disorders and Phenotypes

Operation

- ☒ Union
☐ Intersection

Gene Name

e.g.:BRCA1

Genes selected:

✕ Remove all

Select a predefined gene list

Upload comma separated list of HGNC identifiers

✕

Browse...

No file selected.

Search OMIM

Search OMIM for clinical features, phe

Genes linked to :

✕ Remove All

Search HPO

Enter search terms...

Genes linked to :

✕ Remove All

👤 Fetch HPOs From PhenoTips



Results (integrated data and links)

Samples	Functional	Predictive	Population	Diseasecard	Candidate	Links	ALFA				
Gene Name	Transcript ID	Effect Impact	Consequence	Feature Type	HGVS coding	Amino Acid change	Amino Acid length	Genotype Number	Exon Rank	CDS Position	Transcript BioType
MFAP2	ENST0000037553	MODERATE	missense_variant	transcript	c.313A>C	p.Thr105Pro	183	1	7/9	313/552	protein_coding
MFAP2	ENST0000037553	MODERATE	missense_variant	transcript	c.310A>C	p.Thr104Pro	182	1	6/8	310/549	protein_coding
MFAP2	ENST0000037553	MODERATE	missense_variant	transcript	c.310A>C	p.Thr104Pro	182	1	7/9	310/549	protein_coding

Variants (11)

Exomiser

First

Previous

1

Next

Last

EXPORT ALL

Chr	Pos	dbSNP	Ref	Alt	Candidate	GT ^{E000010}	GT ^{E000036}	GT ^{E000037}	INDEL	Gene Name	Effect Impact	ClinVar	CADD	SIFT	PP2	MT	ExAC	1000GP AF
1	17302199		T	G	0 <div>ADD</div>	T/G	T/T	T/T		MFAP2	MODERATE		26.9	D	D	D	NA	0
11	<div>Ensembl</div>		C	A	0 <div>ADD</div>	C/A	C/C	C/C		OMIM	MODERATE		34	D	D	D	NA	0
13	<div>ExAC</div>		G	A	0 <div>ADD</div>	G/A	G/G	G/G		<div>Ensembl</div>	MODERATE		25.6	T		D	NA	0
13	<div>gnomAD</div>		A	C	0 <div>ADD</div>	A/C	A/A	A/A		<div>PubMed</div>	MODERATE		24.6	D		D	NA	0
13	<div>UCSC</div>		G	T	0 <div>ADD</div>	G/T	G/G	G/G		<div>HGMD</div>	MODERATE		< 20	T		B	NA	0
17	<div>NCBI</div>		A	C	0 <div>ADD</div>	A/C	A/A	A/A		<div>Entrez</div>	MODERATE		26.7	D		P	NA	0
17	<div>DGVa</div>		A	C	0 <div>ADD</div>	A/C	A/A	A/A		<div>GeneCards</div>	MODERATE		21.4	D		D	NA	0
17	<div>GWAS Central</div>		A	C	0 <div>ADD</div>	A/C	A/A	A/A		<div>TMEM132B</div>	MODERATE		20.6	T		B	NA	0
1	<div>GA4GH Beacon</div>		G	C	0 <div>ADD</div>	G/C	G/G	G/G		<div>ClinVar</div>	MODERATE		24.4	D		D	NA	0
1	<div>VarSome</div>		G	C	0 <div>ADD</div>	G/C	G/G	G/G		<div>ExAC</div>	MODERATE		27	T		D	NA	0
22	30768124		T	G	0 <div>ADD</div>	T/G	T/T	T/T		<div>GTEx</div>	MODERATE		< 20	T		P		
X	6451869	rs35874450	C	T	0 <div>ADD</div>	C/T	C/C	C/C		<div>gnomAD</div>	MODERATE	2						
										<div>GWAS Central</div>								
										<div>ATLAS</div>								
										<div>WikiPathways</div>								
										<div>Open PHACTS</div>								

RD

Connect



Exomiser for Variant Prioritisation

34

Variants (9)

Exomiser

Run Exomiser on filtered results

HPO terms are extracted from the first affected sample that is selected. If you want to run the analysis on another sample, please select it as first.

For performance reasons, Exomiser can only run with a number of variants up to 200.

Set Parameters

Inheritance model:

Autosomal dominant

Prioritise genes:

PhenIX (compare phenotypes against human only)

Exomiser will run with the following HPO terms: HP:0000297 HP:0000467 HP:0001252 HP:0001374 HP:0002540 HP:0002783 HP:0002804 HP:0005684

SUBMIT

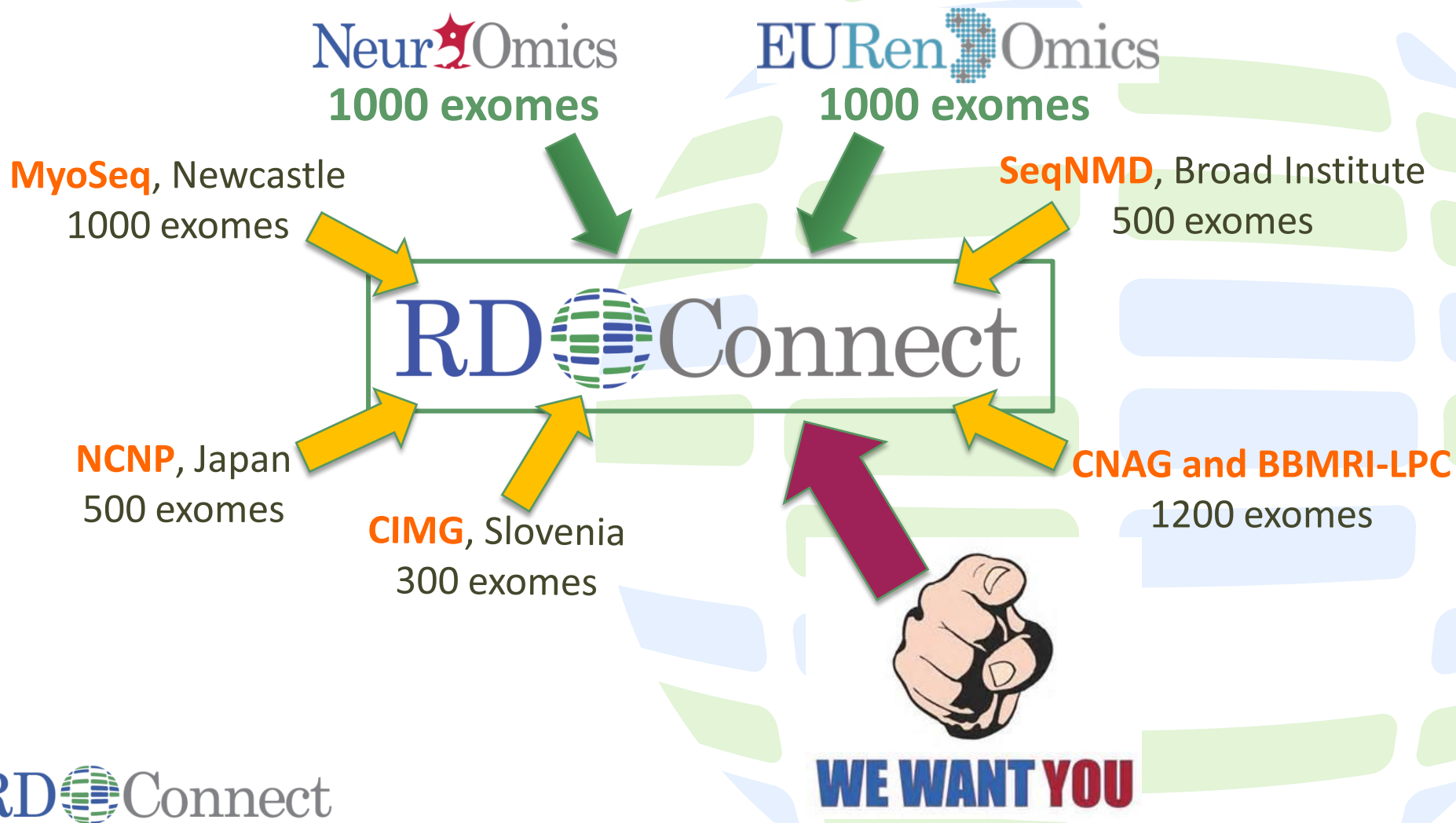
RESULTS

HPO terms and inheritance model extracted from
PhenoTips through API



Data in the RD-Connect GPAP

35





2016 BBMRI-LPC Whole Exome Sequencing Call

36

Sequencing the exome of 900 rare disease samples in collaboration with EuroBioBank and RD-Connect

Objectives

- ✓ to **promote the usage of biobanks for rare diseases**
 - samples deposited in the EuroBioBank network
- ✓ to promote the utilization of NGS for the identification of novel causative variants and genes through **free-of-charge sequencing of 900 exomes**
- ✓ to molecularly diagnose RD patients analysis through the RD-Connect GPAP
- ✓ **to promote data sharing for rare disease research** through the EGA and RD-Connect and phenotyping with HPO



2016 BBMRI-LPC Whole Exome Sequencing Call

37

Sequencing the exome of 900 rare disease samples in collaboration with EuroBioBank and RD-Connect

Eligibility

- ✓ Coordinated projects, with **2-3 PIs from different European countries**
- ✓ Each **project will focus on a particular disorder** and will include at least **3 genetically undiagnosed index cases**
- ✓ Samples must have been obtained with "**informed consent**" of donors, including **sharing of the data in controlled access repositories and databases**
- ✓ DNA **samples must be available in the biobanks from the EuroBioBank network**, or researchers must commit to deposit them , if project is awarded
- ✓ **Phenotypic description of the donors will have to be provided** using the Human Phenotype Ontology (HPO)



2016 BBMRI-LPC Whole Exome Sequencing Call

38

Sequencing the exome of 900 rare disease samples in collaboration with EuroBioBank and RD-Connect

Timeline

Call launch	June 23 rd 2016
Project submission	by July 25 th 2016
Review Process	by September 2 nd 2016
Sample Submission	by September 30 th 2016
Sequencing	by December 30 th 2016
Data release	by February 28 th 2017



2016 BBMRI-LPC Whole Exome Sequencing Call

39

Sequencing the exome of 900 rare disease samples in collaboration with EuroBioBank and RD-Connect

Outcome

- ✓ 17 transnational projects selected
- ✓ 899 samples sequenced in total
- ✓ 10 projects sequenced at CNAG (545 samples)
- ✓ 7 projects sequenced at the Wellcome Trust Sanger Institute (345 samples)



2016 BBMRI-LPC Whole Exome Sequencing Call

TITLE OF AWARDED PROJECT	PRINCIPAL INVESTIGATORS
Exome sequencing of a cohort of Rett syndrome-like patients	Armstrong Morón JS, Tejada M, Renieri A
Genetic Heterogeneity of the familial gastric neuroendocrine tumors	Benitez J, Valdés Socin H, Calvete O
Molecular diagnosis of albinism	Montoliu José L, Carracedo Alvarez Á, Arveiler B
Deciphering the molecular causes of Ophthalmogenetic Diseases : Exome Sequencing analysis for gene discovery	Ayuso C, Rivolta C
Exome trios in 50 patients with gastroschisis	Lapunzina P, Scarano G
Identification of novel genes in patients with Congenital Myasthenic Syndrome (CMS)	Lochmüller H, Senderek J
Identification of Molecular Pathology of Undiagnosed Patients with Mitochondrial Disorders by Whole Exome Sequencing	Dursun A, Soler D
Undiagnosed cases with complex phenotypes including intellectual disability	Posada De La Paz M, Forzano F, Mari F
Identification of Genetic Causes of Undiagnosed Epileptic Encephalopathies	Yalnizoglu D, Antonietta Mencarelli M, Koksall Ozgul R
Unravelling the genetic cause of a neuropathic pain phenotype segregating in an extended multigenerational family through WES	Cormand Rifà B, Serra J
Identification of genes involved in congenital disorders of glycosylation and 3-methylglutaconic aciduria	Tort F, Morava Kozicz E, Vilarinho L
Undiagnosed cases of congenital and dystrophic neuromuscular diseases	Mora M, Muntoni F, Scerri C
Gene Characterization in Carbohydrate metabolic alterations (neonatal diabetes & congenital hyperinsulinemic) in early childhood	Castañó L, Barbetti F, Polak M
Identification and characterization of the underlying genetic and molecular defect in undiagnosed inherited ataxias by WES	Matilla-Dueñas A, Houlden HJ
Whole exome sequencing for clarification of rare causes of axonal Charcot-Marie-Tooth disease	Espinós C, Seeman P
Identification of additional genes involved in Pyruvate Kinase Deficiency phenotypic variability	Segovia JC, Bianchi P, van Wijk R
Identification of New Genes involved in Infant and Adult Sudden Cardiac Death	Gimeno Blanes JR, Corral De La Calle J, Elliott PM

BBMRI-LPC exome call: Preliminary Results

PROJECT	PI.1	CLINICAL REFERRAL	TOTAL SAMPLES	TOTAL FAMILIES	PEDIGREES ANALYSED	TOTAL CASES WITH CANDIDATE VARIANTS (ALL)	TOTAL CASES WITH CANDIDATE VARIANTS (%)	TOTAL VERY STRONG CANDIDATES	TOTAL VERY STRONG CANDIDATES (%)
BBMRI_01	Carmen Ayuso	Ophthalmogenetic Diseases	41	10	10	4	40	4	40
BBMRI_02	Hanns Lochmuller	Congenital Myasthenic Syndrome	87	47	47	16	34	16	34
BBMRI_03	Ali Dursun	Mitochondrial Disorders	50	41	41	25	61	19	46
BBMRI_04	Manuel Posada	Intellectual disability	60	26	8	5	62,5	4	50
BBMRI_05	Dilek Yalnizoglu	Epileptic Encephalopathies	50	32	32	19	59	12	37
BBMRI_06	Bru Cormand	Neuropathic pain	15	1	1	0	0	0	0
BBMRI_07	Marina Mora	Neuromuscular diseases	81	52	52	24	46	13	25
BBMRI_08	Antonio Matilla	Ataxia	50	28	28	16	57	11	39
BBMRI_09	José C. Segovia	Pyruvate Kinase Deficiency	31	Not released					
BBMRI_10	JR Gimeno Blanes	Sudden Cardiac Death	83	Pending					

Total	548	237	219	109	50	79	36
--------------	-----	-----	-----	-----	----	----	----

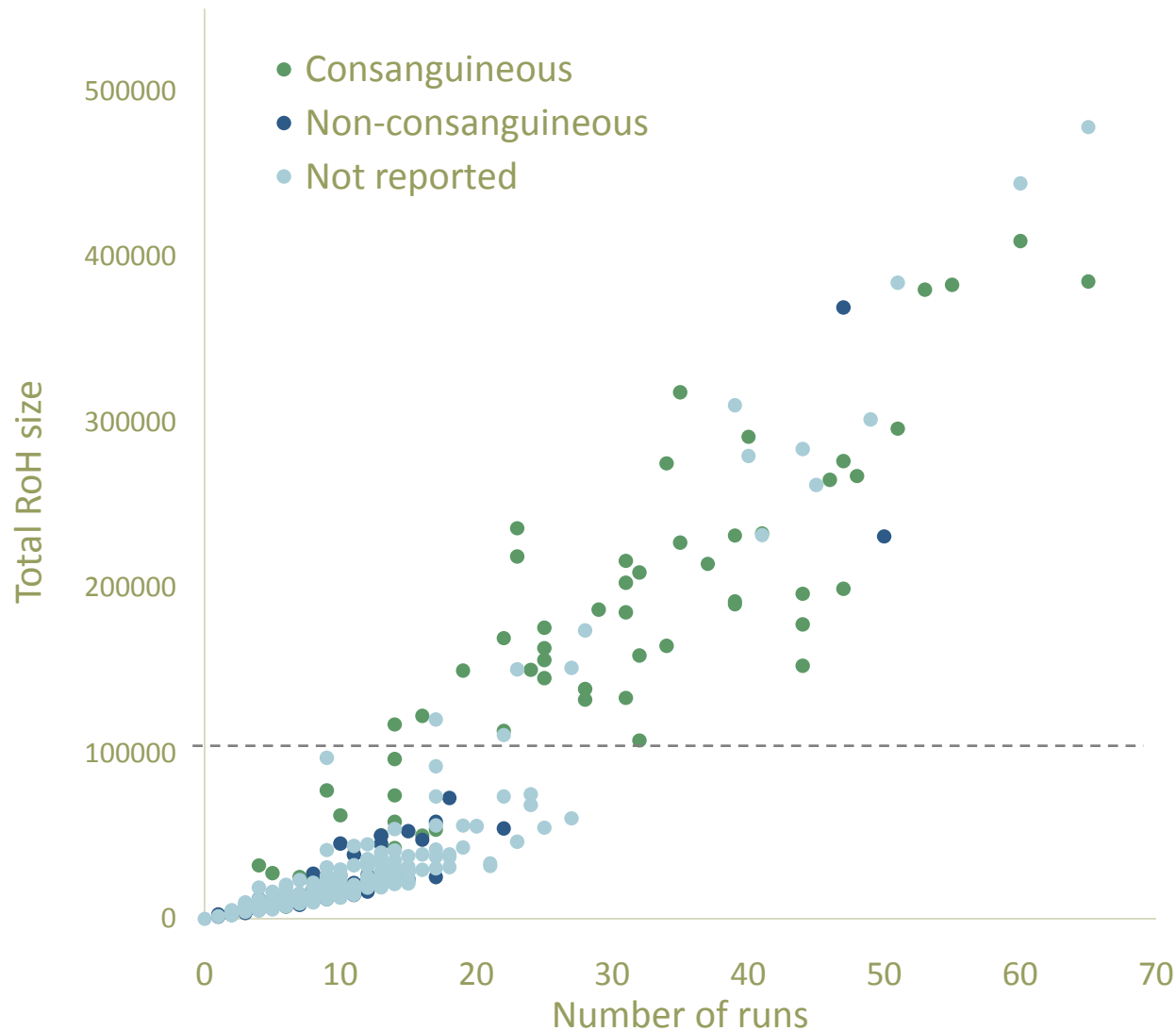
CANDIDATE VARIANTS

Very good candidates + VUS in described genes or P and LP in genes associated with diseases that partially fit the clinical symptoms-> need validation from clinician

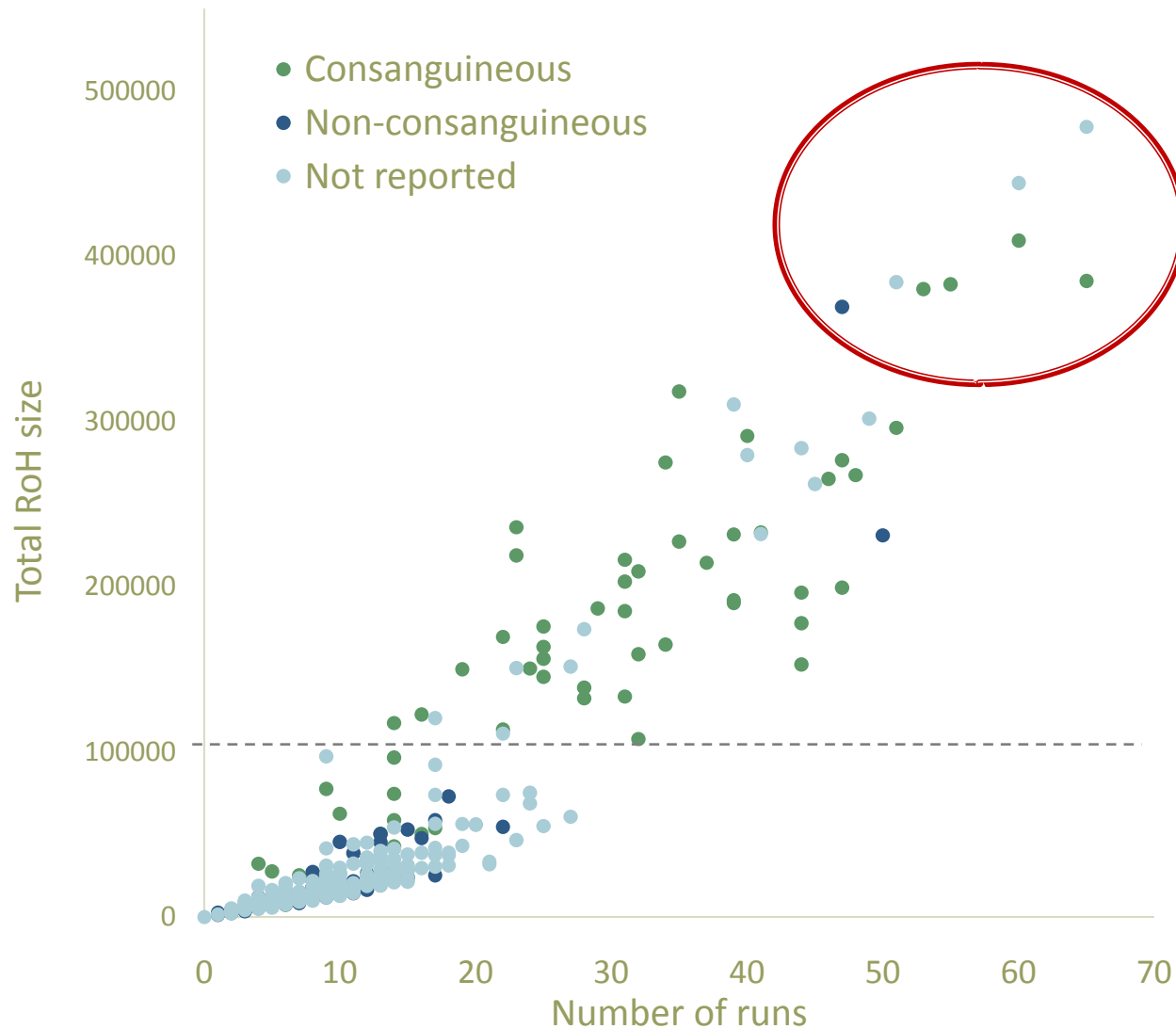
VERY STRONG CANDIDATES

P or LP variants in described genes or VUS in described genes that fit the phenotype of the patient

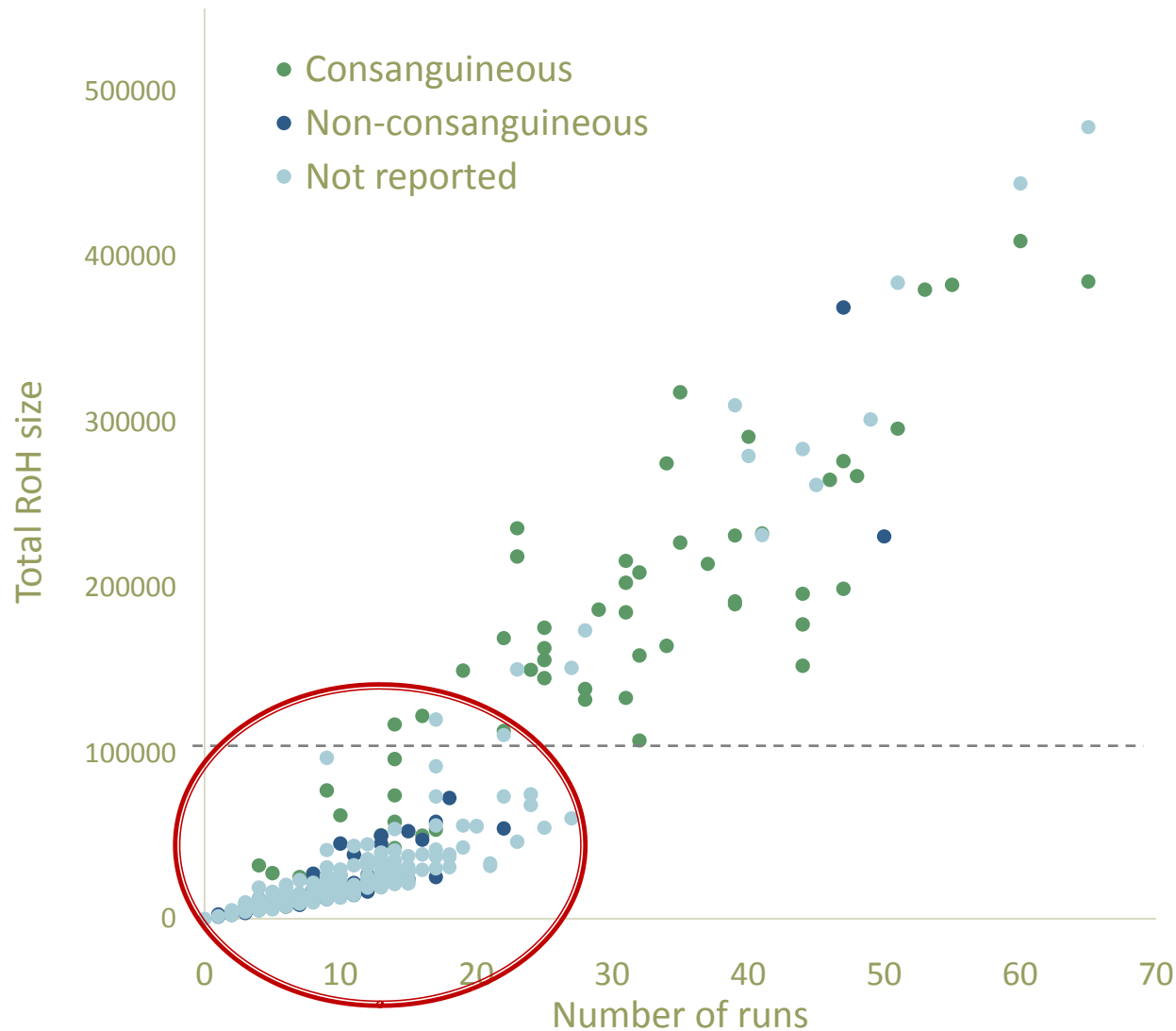
Concordance of length of RoH with consanguinity reported in PhenoTips



Concordance of length of RoH with consanguinity reported in PhenoTips



Concordance of length of RoH with consanguinity reported in PhenoTips





Standard filters – 101 variants

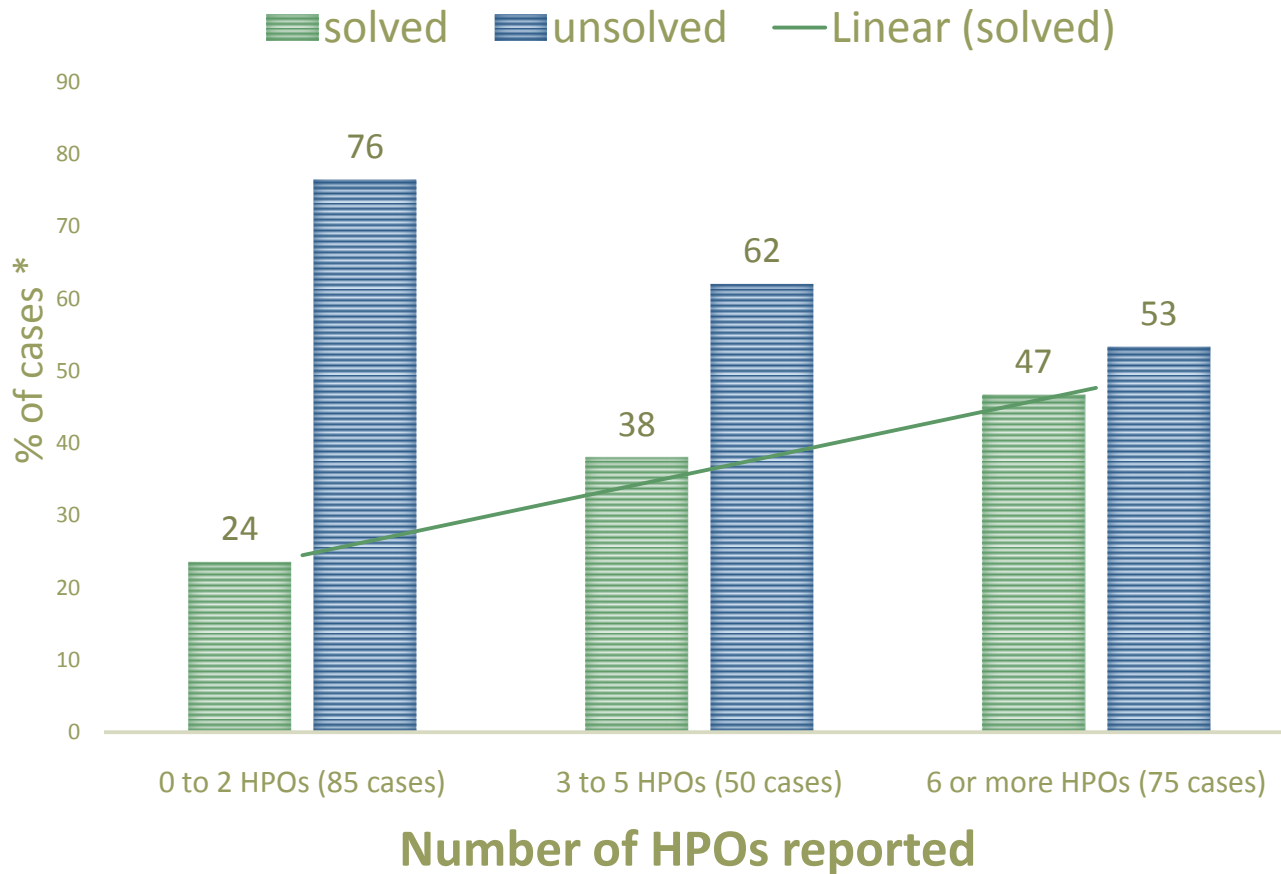
Homozygous blocks – 9 variants

[illegible]

17	4805260	G	A	A/A	A/A	CHRE	MODERATE	32	D	D	D	NA	0
----	---------	---	---	-----	-----	------	----------	----	---	---	---	----	---

Importance of Detailed Phenotypic Description

PERCENTAGE OF RESOLUTION OF CASES VS NUMBER OF REPORTED HPOS





RD-Connect: Become a partner

47

- Registration details are available on-line – first point of contact is platform@rd-connect.eu
- Check your consent forms - do they cover data sharing for research purposes?
- Check your phenotypic data - do you have a detailed phenotype for each participant?
- Check your data - do you have access to the BAM / CRAM / FastQ files from your sequencing experiments?
- Contact us - platform@rd-connect.eu for further details



Acknowledgements

48

WP1: Coordination

Hanns Lochmüller

(Newcastle and TREAT-NMD)

WP2: Patient registries

Domenica Taruscio (ISS and EPIRARE)

WP3: Biobanks

Lucia Monaco

(Fondaz. Telethon & EuroBioBank)

WP4: Bioinformatics

Christophe Bérout

(INSERM, Marseille)

WP5: Unified platform

Ivo Gut (CNAG, Barcelona)

WP6 Ethical/legal/social

Mats Hansson (Uppsala)

WP7: Impact/Innovation

Kate Bushby

(Newcastle and EUCERD/ EJARD)

CNAG

I. Gut

S. Beltran

D. Piscia

S. Laurie

J. Protasio

A. Papakons.

F. Camacho

I. Martinez

L. Matalonga

R. Tonda

J.R. Trotta

CNIO/BSC

A. Valencia

S. Capella

J.M. Fernández

U. Aveiro

J.L. Oliveira

P. Lopes

P. Sernaleta

AMU

C. Bérout

D. Salgado

J.P. Desvignes

Interactive BioSoftware

A. Blavier

S. Lair

EGA

D. Spalding

J. Almeida-King

A. Navarro

J. Rambla

Newcastle U.

H. Lochmüller

R. Thompson

J. Dawson

D. Badowska

A. Topf

LUMC

P.B. t'Hoen

M. Roos

R. Raliyaperumal

M. Thompson

Murdoch U. U. of Patras

M. Bellgard

G. Patrinos

MME

H. Rehm

U. Of Toronto

M. Brudno

O. Buske

M. Girdea

S. Dumitriu

cnag

CRG
Centre
for Genomic
Regulation



bbmri-lpc





Try it for yourself

49

**RD-Connect GPAP Hands-on demos
today at 1415h and 1615h
In Zurich 3**



If you would like to join RD-Connect, please contact
platform@rd-connect.eu

RD-Connect: <http://rd-connect.eu/>  @ConnectRD

Facebook: <https://www.facebook.com/rdconnect>

Platform: <https://platform.rd-connect.eu/>

Other sequencing and data analysis projects:

projectmanager@cnag.crg.eu

cnag

centre nacional d'anàlisi genòmica
centro nacional de análisis genómico



steven.laurie@cnag.crg.eu

 @SteveLaurie42

