

Solving RDs with the RD-Connect Genome- Phenome Analysis Platform

Sergi Beltran and Leslie Matalonga

cnag

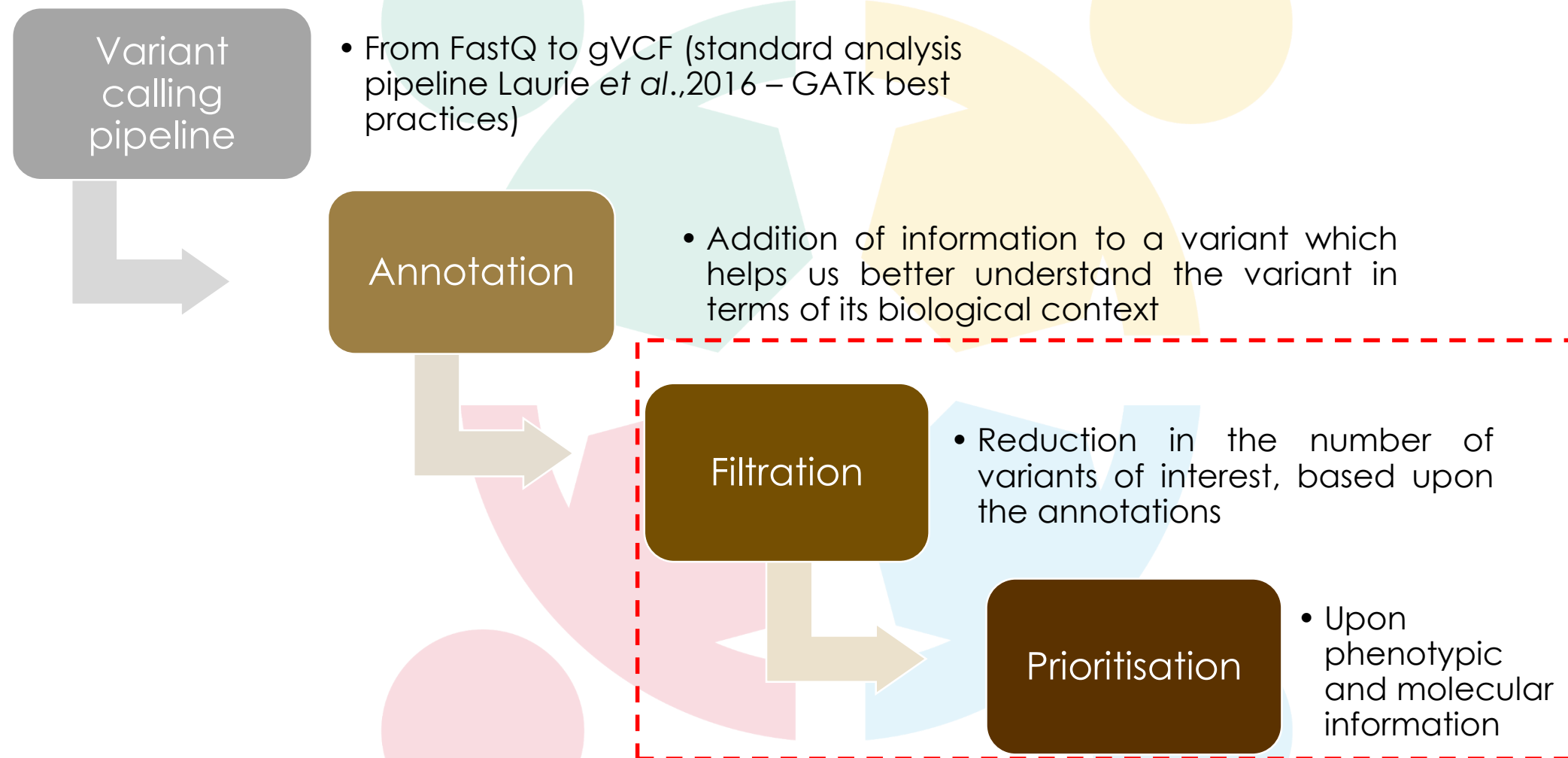


```
O|O:123:123,123 O|O:123:123,123 O|1:123:123,123 O|1:49:52,5
123,123 O|O:123:123,123 O|O:123:123,123 O|O:123:123,123 O|O:52:123,
O|O:123:123,123 O|O:123:123,123 O|O:123:123,123 O|O:123:123,123
123,123 O|1:123:123,123
O|O:123:123,123 1|O:123:123,123:56;0.0852854;21;19 O|O:123:123
O|O:123:123,123 O|O:83:83,123 O|1:43:123,43 O|O:123:123,123 O|O
123,123 1|O:68:68,123 O|O:123:123,123 O|O:123:123,123 O|O
O|O:51:123,51 O|O:43:43,123 O|O:87:123,87 O|O:114:123
123,123 1|O:37:37,123 O|O:123:123,123 O|O:123:123,123 O|O
O|O:123:123,123 1|O:123:123,123
O|O:123:123,123 O|O:123:123,123:59;0.102882;5;3 O|O:113:123
123,123 O|O:123:123,123 O|O:123:123,123 O|O:76:105,76 O|O
O|1:123:123,123 O|O:76:76,123 O|O:123:123,123 O|O:123:123
123,123 O|O:123:123,123 O|O:123:123,123 1|O:123:123,123
O|O:123:123,123 1|O:123:123,123 O|1:106:123,106
123,123 O|O:113:123,113
Q1,HQ2 O|O:123:1
```

```
ro@n8 indelcalling]$ awk 'print $1$2' caca.vcf
syntax error
^ backslash not last character on line
ro@n8 indelcalling]$
```

```
ro@n8: /COPY temp/indelcalling
help! for more information.
scratch/devel/fcastro/data/1000genomes/indelcalling/CEU* .
```

Molecular diagnostic and gene discovery challenge



Genome - Phenome Analysis Platform

RDConnect

GENOMICS

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ABOUT

{PLATFORM V1.7.3, DATASET PLAY20181003 }

TEST

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Filters

PRESET FILTERS

RESET

SHARE

RUN QUERY

Sample Selection

Select individual Samples or search across all (accessible: 27, own: 0, shared: 0, visible to all: 27)

Variant Type

Population

SNV Effect Prediction

Genes, Disorders and Phenotypes

Position Specific filters and Runs Of Homozygosity

Samples

Functional

Predictive

Population

Pathways

Protein interaction

Diseasecard

Candidate

Links

ALFA

RD-Connect ID	Participant ID	GT	GQ	DP	AAF
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Phenotype

Analysis status

Variants ()

Exomiser

Phenotips id	External id	Gender	Clinical status*	Inheritance	Consanguinity	Genes	Family	Pedigree	Relatives	OMIM disorder	ORDO disorder	HPO terms
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1. SAMPLES

2. FILTERS

3. RESULTS



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--------------	-------------	--------	------------------	-------------	---------------	-------	--------	----------	-----------	---------------	---------------	-----------


1. SAMPLES

2. FILTERS
















3. RESULTS

Samples, inheritance and quality parameters

Sample Selection ⓘ

Select individual Samples  or search across all ☐ ⓘ (accessible: 15, own: 0, shared: 0, visible to all: 15)

☐ ⓘ Compound het.


Affected	Experiment ID	Phenotips	MME	REF/REF	REF/ALT	ALT/ALT	Min Depth	Min Genotype Quality	Min Alternate Allele Freq	Max Alternate Allele Freq	
<input checked="" type="checkbox"/>	Case1C P0007498	P ⓘ		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	10 	30 	0.2 	0.8 	
<input type="checkbox"/>	Case1F P0007499	P ⓘ		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	10 	30 	0.2 	0.8 	
<input type="checkbox"/>	Case1M P0007500	P ⓘ		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	10 	30 	0.2 	0.8 	

Genotypes –
mode of inheritance

Quality
parameters

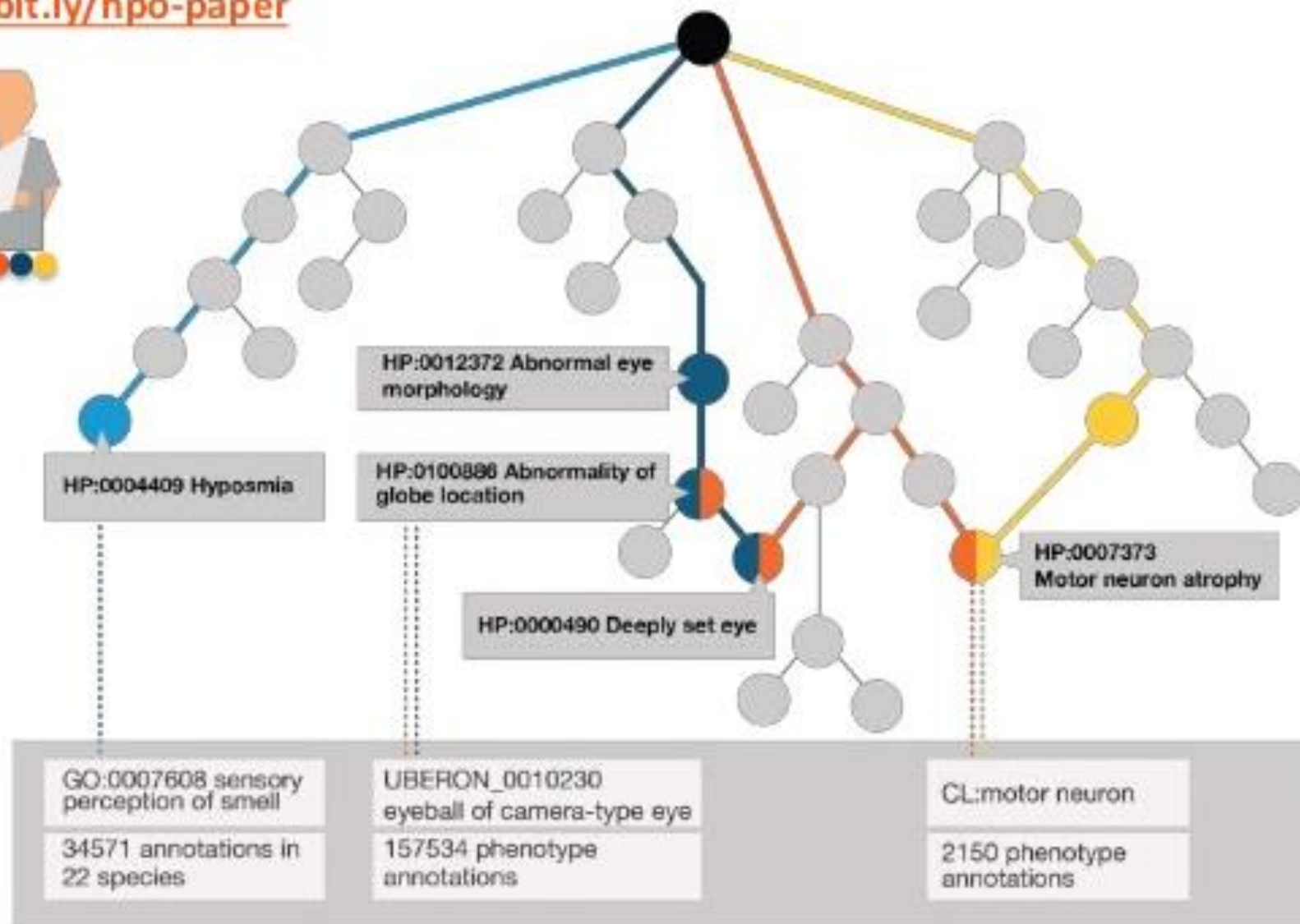
Samples, inheritance and quality parameters

Summary of the patient phenotypic information

Phenotype		Analysis status	Variants ()	Exomiser						
Phenotips id	External id	Gender	Clinical status*	Inheritance	Consanguinity	Genes	Family	Pedigree	ORDO disorder	HPO terms
P0007498	Case1C	Male	Affected	Sporadic	false	unknown	FAM0001814		Congenital myopathy	Neck muscle weakness Muscular hypotonia Neonatal hypotonia Congenital hip dislocation Inability to walk Recurrent lower respiratory tract infections Arthrogryposis multiplex congenita Skeletal muscle atrophy Distal arthrogryposis Weakness of facial musculature NO Intellectual disability

Human Phenotype ontology: what is an HPO?



bit.ly/hpo-paper


















- Standardised vocabulary of phenotypic abnormalities
- Tree based classification – symptom granularity
- Developed using medical literature: Orphanet, OMIM and Decipher
- Terms are mapped with other ontologies (e.g. GO)
- Currently comprises more than 13,000 terms and over 156,000 annotations to hereditary diseases

Samples, inheritance and quality parameters

Sample Selection ⓘ

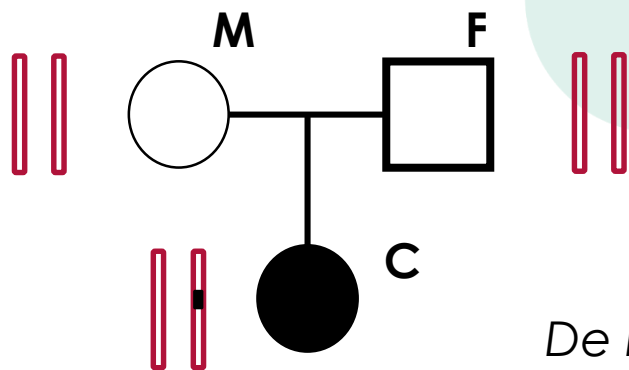
Select individual Samples  or search across all  (accessible: 15, own: 0, shared: 0, visible to all: 15)

Affected	Experiment ID	Phenotips	MME	<input type="checkbox"/> ⓘ Compound het.	REF/REF	REF/ALT	ALT/ALT	Min Depth	Min Genotype Quality	Min Alternate Allele Freq	Max Alternate Allele Freq	
<input checked="" type="checkbox"/>	Case1C P0007498	P ⓘ		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	10 	30 	0.2 	0.8 	
<input type="checkbox"/>	Case1F P0007499	P ⓘ		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	10 	30 	0.2 	0.8 	
<input type="checkbox"/>	Case1M P0007500	P ⓘ		<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	10 	30 	0.2 	0.8 	

Genotypes –
mode of inheritance

Quality
parameters

Genotypes and mode of inheritance

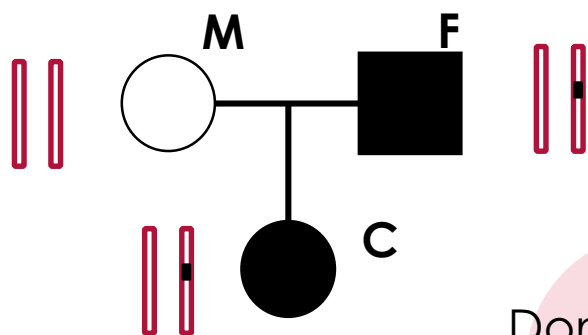


De novo

Affected Experiment ID

☒ Index case
☐ Mother
☐ Father

REF/REF	REF/ALT	ALT/ALT
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



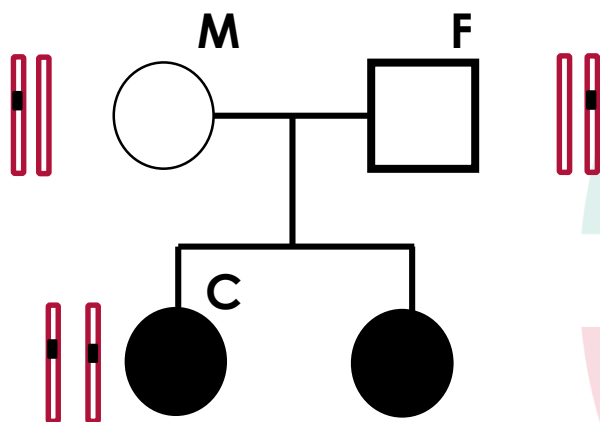
Dominant

Affected Experiment ID

☒ Index case
☐ Mother
☒ Father

REF/REF	REF/ALT	ALT/ALT
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Genotypes and mode of inheritance



Autosomal recessive

Affected	Experiment ID	REF/REF	REF/ALT	ALT/ALT
<input checked="" type="checkbox"/>	Index case	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/>	Mother	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Father	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Affected	Experiment ID	REF/REF	REF/ALT	ALT/ALT
<input checked="" type="checkbox"/>	Index case	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Mother	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Father	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

☒ **Compound het.**

Genome - Phenome Analysis Platform

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Filters

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Sample Selection

Select individual Samples or search across all (accessible: 27, own: 0, shared: 0, visible to all: 27)

Variant Type

Population

SNV Effect Prediction

Genes, Disorders and Phenotypes

Position Specific filters and Runs Of Homozygosity

Samples

Functional

Predictive

Population

Pathways

Protein interaction

Diseasecard

Candidate

Links

ALFA

RD-Connect ID	Participant ID	GT	GQ	DP	AAF
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Phenotype

Analysis status

Variants ()

Exomiser

Phenotips id	External id	Gender	Clinical status*	Inheritance	Consanguinity	Genes	Family	Pedigree	Relatives	OMIM disorder	ORDO disorder	HPO terms
--------------	-------------	--------	------------------	-------------	---------------	-------	--------	----------	-----------	---------------	---------------	-----------

1. SAMPLES

2. FILTERS

3. RESULTS



Filtering steps

Variant Type ⓘ

Variant Class

☐ High
☐ Moderate
☐ Low
☐ Modifier

ClinVar Classification

☐ Pathogenic
☐ Likely pathogenic
☐ Variant of uncertain significance
☐ Conflicting interpretations
☐ Drug response
☐ Any

Variant Type

☐ SNV
☐ INDEL

Transcript Biotype

☐ Protein_coding
☐ RNA
☐ Other

Tagged Variants

☐ Selected samples
☐ Any samples

As defined by SnpEFF - see [Effect prediction details](#) section for a detailed explanation

Population ⓘ

SNV Effect Prediction ⓘ

Genes, Disorders and Phenotypes

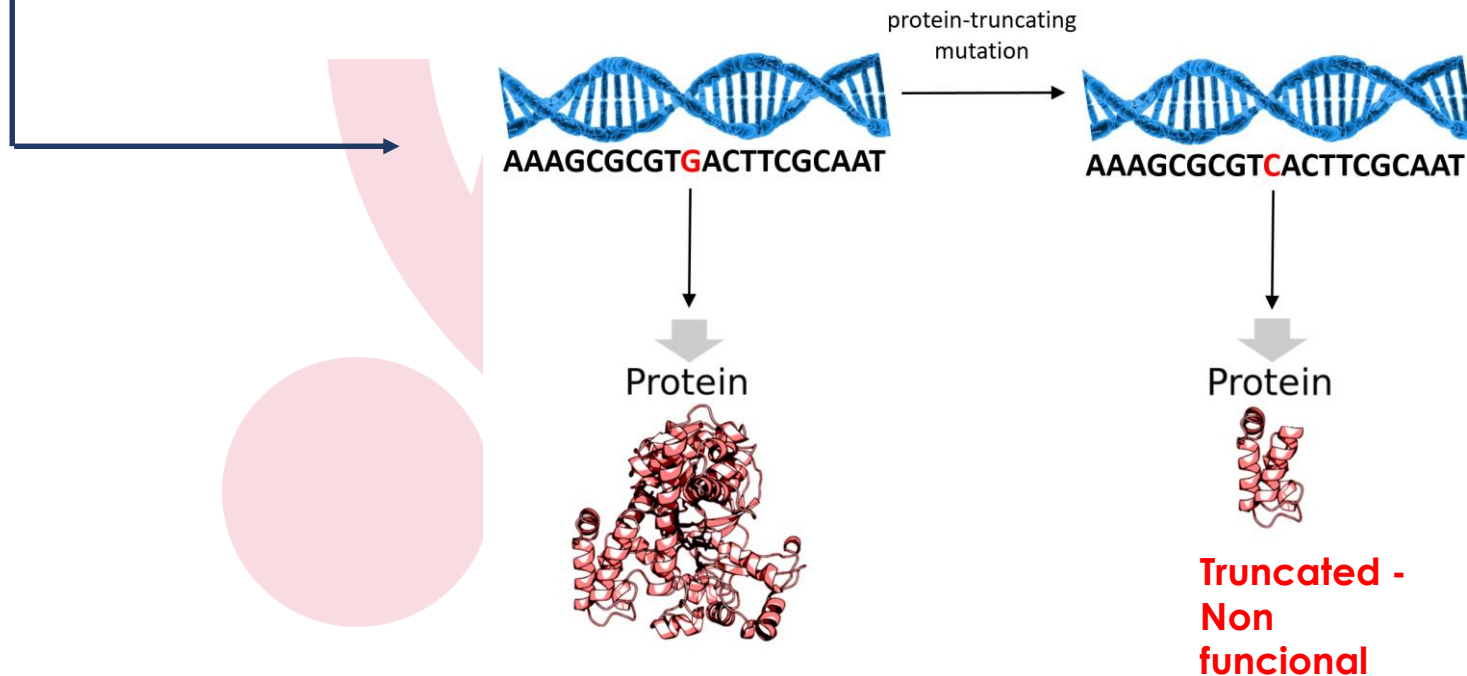
Position Specific filters and Runs Of Homozygosity

Hover the cursor
over the text to see
tool tips that
explain the field

Filtering steps- variant consequence

SnEff/ VEP categorise all variants into one of four impact categories (variant consequence annotation)

HIGH	Variants significantly affect protein structure e.g. nonsense, frameshift, canonical splice-sites
MODERATE	Mainly non-synonymous variants i.e. amino-acid change
LOW	Mainly synonymous variants i.e. no amino acid change
MODIFIER	Mutations in non-coding regions



Source: <http://thedishonscience.stanford.edu/posts/essential-genes/>

Filtering steps, tools and databases

Databases of allele frequencies in **control** populations allows us to estimate how common or rare a particular variant may be.



FILTER FOR VARIANT PRESENT IN LESS THAN 1% OF ALLELES

Population ⓘ

ExAC

1000GP AF

Internal Freq

gnomAD AF

gnomAD filter status
☐ PASS + unannotated (NA)
☐ non-PASS

Filtering steps, tools and databases

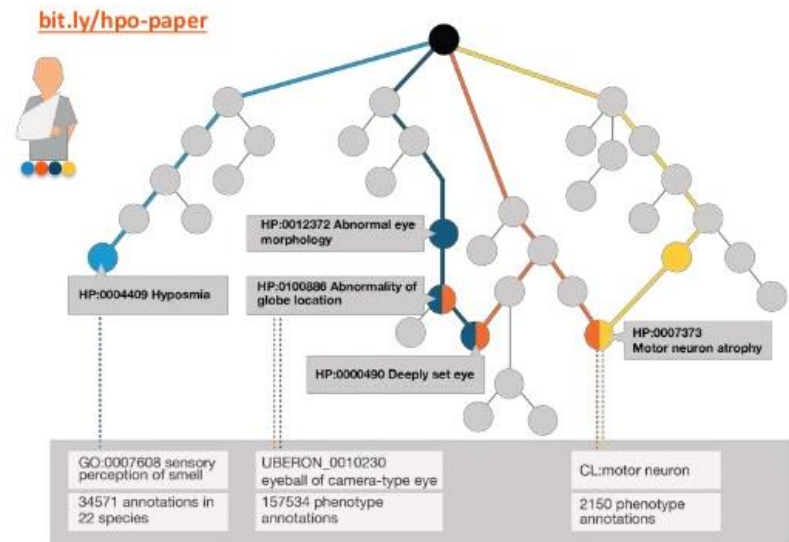
Filter using a list of candidate genes generated on-the-fly

Genes in the panel: ACTA1, BIN1, CACNA1S, CFL2, COL12A1, COL6A1, COL6A2, COL6A3, DNM2, EPG5, FKBP14, HTRA2, KBTBD13, KLHL40, KLHL41, LGI4, LMNA, LMOD3, MAP3K20, MEGF10, MICU1, MTM1, MYH2, MYH3, MYH7, MYH8, MYMK, MYO18B, NEB, ORAI1, RYR1, SCN4A,



Filtering steps, tools and databases

Filter using a list of candidate genes generated on-the-fly



Virtual gene panel based on HPOs

1. Select HPO term(s)

Search HPO...

Fetch patient HPOs From PhenoTips

Remove All

List of HPOs:

2. Build a gene list based on the following resource:

Resources:

HPO ontology

Mendelian.co

DisGeNET

Remove All

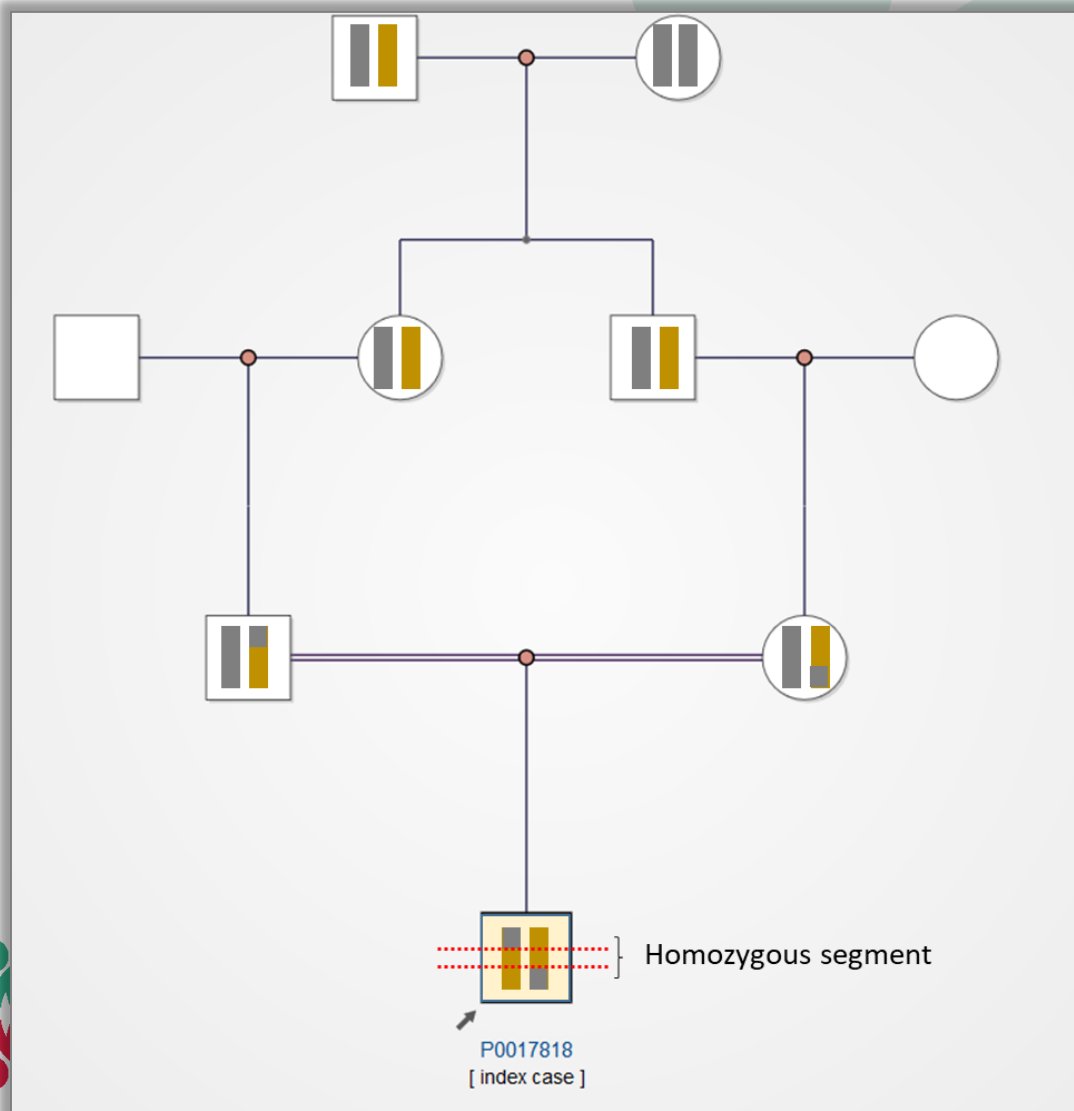
Genes added to:

PATIENT SYMPTOMS

Filtering steps, tools and databases

Filter to Regions of Interest (ROI) and/or regions containing long Runs of Homozygosity (Absence of Heterozygosity)

Filter to only variants found within a RoH- particularly useful when consanguinity is suspected.



and Runs Of Homozygosity

Minimum run of homozygosity length

☐ 0.5MB

☐ 1.0MB

☐ 2.0MB

Upload coordinate file

No file selected.

Filtering steps, tools and databases

RUN your QUERY to see the results

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Filters

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Variant Type: high moderate

Population: exac

Genes: hpo

Summary of filters

Sample Selection

Select individual Samples or search across all (accessible: 27, own: 0, shared: 0, visible to all: 27)

☐ Compound het.

Affected	Experiment ID	Phenotips	MME	REF/REF	REF/ALT	ALT/ALT	Min Depth	Min Genotype Quality	Min Alternate Allele Freq	Max Alternate Allele Freq	
<input checked="" type="checkbox"/>	Case1C P0007498	P1		<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	10	30	0.2	0.8	X

Variant Type

Population

SNV Effect Prediction

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Sample Selection

Select individual Samples or search across all (accessible: 27, own: 0, shared: 0, visible to all: 27)

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RD-Connect ID	Participant ID	GT	GQ	DP	AAF
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Phenotype

Analysis status

Variants ()

Exomiser

Phenotips id	External id	Gender	Clinical status*	Inheritance	Consanguinity	Genes	Family	Pedigree	Relatives	OMIM disorder	ORDO disorder	HPO terms
--------------	-------------	--------	------------------	-------------	---------------	-------	--------	----------	-----------	---------------	---------------	-----------

1. SAMPLES

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Results section

Multiple tabs with detailed information for data interpretation

Samples Functional Predictive Population Pathways Protein interaction Diseasecard Candidate Links ALFA										
Gene Name	Transcript ID	Effect Impact	Consequence	Feature Type	HGVS coding	Amino Acid change	Amino Acid length	Exon Rank	CDS Position	Transcript BioType
HFM1	ENST00000370425	HIGH	frameshift_variant	transcript	c.255delA	p.Leu86Ter	1435	4/39	255/4308	protein_coding
HFM1	ENST00000427444	HIGH	frameshift_variant	transcript	c.129delA	p.Leu44Ter	196	3/4	129/591	protein_coding
HFM1	ENST00000455133	HIGH	frameshift_variant	transcript	c.255delA	p.Leu86Ter	138	4/4	255/417	protein_coding

Phenotype		Analysis status		Variants (22)		Exomiser																				
		First		Previous		1		Next		Last																
Chr	Position	dbSNP	Ref	Alt	Candidate	GT Case1C	GT Case1F	GT Case1M	INDEL	Gene	Effect Impact	ClinVar	CADD	SIFT	PP2	MT	ExAC	1000GP AF	gnomAD AF	Internal Freq						
1	91859888	.	GT	G	0 TAG	GT/G	GT/GT	GT/GT	☑	HFM1	HIGH		< 20				NA	NA	NA	0.166667						
1	225477618	.	G	C	0 TAG	G/C	G/G	G/G		DNAH14	MODERATE		23.1	D	P	N	NA	NA	NA	0.166667						
2	233349186	.	G	A	0 TAG	G/A	G/G	G/G		ECEL1	MODERATE		23.4	D	B	N	NA	NA	NA	0.166667						

Results section

Phenotype		Analysis status		Variants (22)		Exomiser														
First		Previous		1		Next		Last												
Chr	Position	dbSNP	Ref	Alt	Candidate	GT Case1C	GT Case1F	GT Case1M	INDEL	Gene	Effect Impact	ClinVar	CADD	SIFT	PP2	MT	ExAC	1000GP AF	gnomAD AF	Internal Freq
1	91859888		GT	G	0 TAG	GT/G	GT/GT	GT/GT	✓	HFM1	HIGH		< 20				NA	NA	NA	0.166667
Ensembl			G	C	0 TAG	G/C	G/G	G/G		OMIM	MODERATE		23.1	D	P	N	NA	NA	NA	0.166667
ExAC			G	A	0 TAG	G/A	G/G	G/G		Ensembl	MODERATE		23.4	D	B	N	NA	NA	NA	0.166667
gnomAD		60722486	C	G	0 TAG	C/G	C/C	C/C		PubMed	MODERATE		< 20				NA	NA	NA	0.166667
UCSC			G	A	0 TAG	G/A	G/G	G/G		FARF2	MODERATE		< 20	T	B	N	0.000025	NA	0.000094	0.166667
NCBI			A	C	0 TAG	A/C	A/A	A/A		HGMD	MODERATE		24.0	D	D	N	NA	NA	NA	0.166667
DGVA			T	A	0 TAG	T/A	T/T	T/T		MUC20	MODERATE		26.2	D	D	N	NA	NA	NA	0.166667
GWAS Central			T	C	0 TAG	T/C	T/T	T/T		Entrez	MODERATE		23.5	D	P	D	NA	NA	NA	0.166667
GA4GH Beacon		73132598	G	A	0 TAG	G/A	G/G	G/G		GeneCards	MODERATE		24.8	D	D	D	0.000033	NA	0.000033	0.166667
VarSome			TAG	T	0 TAG	TAG/T	TAG/TAG	TAG/TAG	✓	COSMIC	MODERATE		< 20				NA	NA	0.000482	0.166667
			G	GTTTTTTTTT..	0 TAG	G/GTTTTTTTTT..	G/G	G/G	✓	ClinVar	MODERATE		< 20				NA	NA	0.000095	0.166667
			T	G	0 TAG	T/G	T/T	T/T		ExAC	MODERATE		< 20				0.000480	NA	NA	0.166667

Links to multiple databases

Results section

e.g direct link to VARSOME – ACMG classification

Verdict
Pathogenic

Transcript [NM_006017.2](#), canonical, protein length 866, gene [PROM1](#), splicing variant

Rules

<input checked="" type="checkbox"/> PVS1	<input type="checkbox"/> PS1	<input type="checkbox"/> PS2	<input type="checkbox"/> PS3	<input type="checkbox"/> PS4	<input type="checkbox"/> PM1	<input checked="" type="checkbox"/> PM2	<input type="checkbox"/> PM3
<input type="checkbox"/> PM4	<input type="checkbox"/> PM5	<input type="checkbox"/> PM6	<input type="checkbox"/> PP1	<input type="checkbox"/> PP2	<input checked="" type="checkbox"/> PP3	<input type="checkbox"/> PP4	<input type="checkbox"/> PP5
<input type="checkbox"/> BA1	<input type="checkbox"/> BS1	<input type="checkbox"/> BS2	<input type="checkbox"/> BS3	<input type="checkbox"/> BS4			
<input type="checkbox"/> BP1	<input type="checkbox"/> BP2	<input type="checkbox"/> BP3	<input type="checkbox"/> BP4	<input type="checkbox"/> BP5	<input type="checkbox"/> BP6	<input type="checkbox"/> BP7	

Please tick or untick any rules to switch them on or off - the Verdict will update.

Identified criteria

Rule	Pathogenicity	Explanation
PVS1	Pathogenic Very Strong	Null variant (within ± 2 of splice site) affecting gene PROM1, which is a known mechanism of disease (gene has 28 known pathogenic variants which is greater than minimum of 5), associated with Cone-rod dystrophy 12, Macular dystrophy, retinal, 2, Stargardt disease 4 and Retinitis pigmentosa 41.
PM2	Pathogenic Moderate	GnomAD exomes allele frequency = 0.0000161 is less than 0.0001 threshold for recessive gene PROM1 (good GnomAD exomes coverage = 75.1). Variant not found in GnomAD genomes (good GnomAD genomes coverage = 32.6).
PP3	Pathogenic Supporting	Pathogenic computational verdict because 3 pathogenic predictions from DANN, FATHMM-MKL and MutationTaster vs no benign predictions.

Results section

Use Exomiser (IRDiRC recognised resource) to prioritise variants according to patient's HPO terms

Phenotypes

Variants (188)

Exomiser

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 recessive

Prioritise genes:

PhenIX (compare phenotypes against human only)

Add HPO:

e.g.:0002356

✕ REMOVE ADDED HPO TERMS

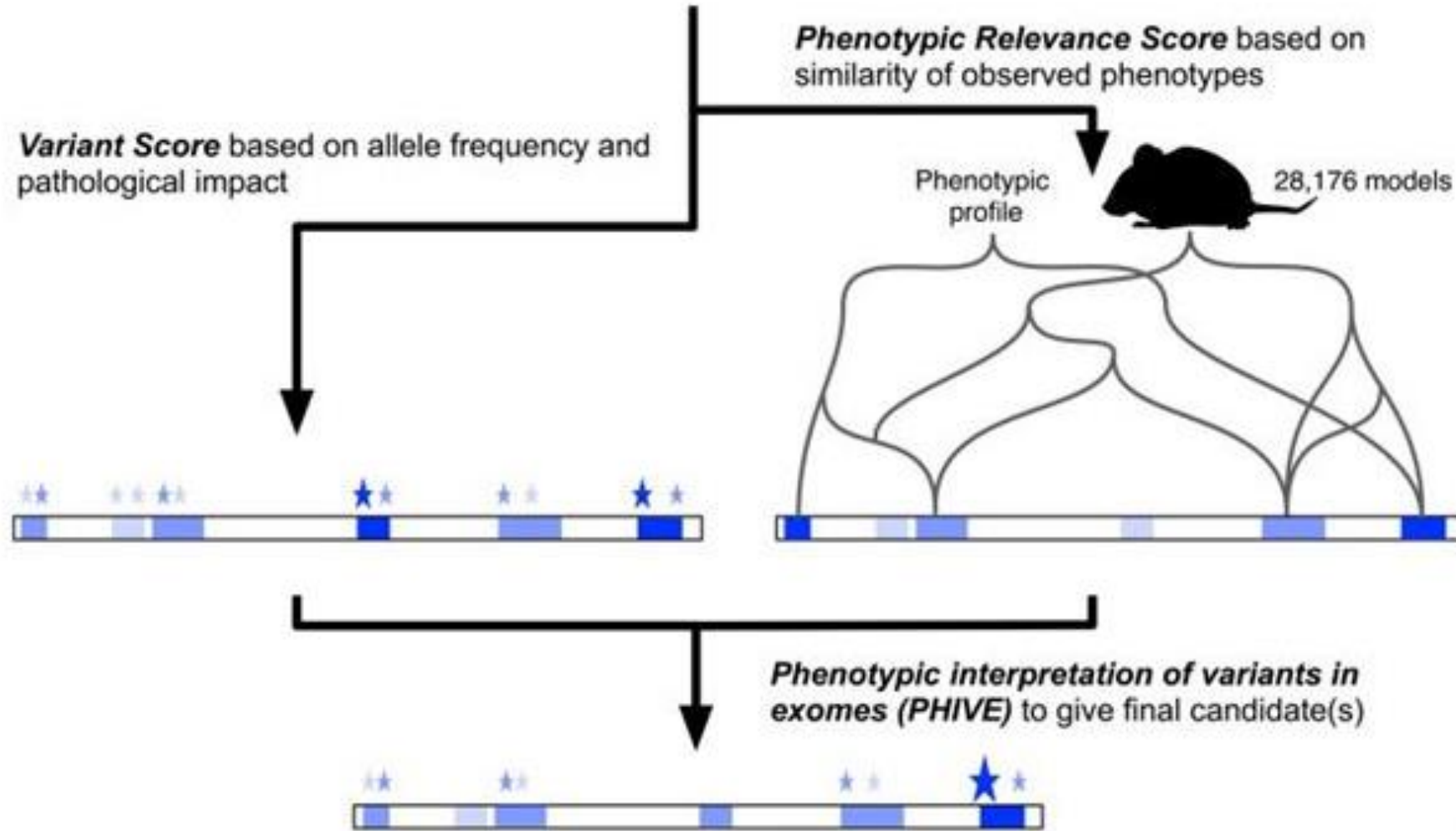
Exomiser will run with the following HPO terms: [HP:0003128](#) [HP:0010964](#) [HP:0200125](#) [HP:0003535](#) [HP:0003344](#) [HP:0004359](#) [HP:0000252](#) [HP:0000488](#) [HP:0001250](#) [HP:0001290](#) [HP:0001644](#) [HP:0002361](#) [HP:0003198](#) [HP:0010531](#)

SUBMIT

RESULTS

Results section

Use Exomiser (IRDiRC recognised resource) to prioritise variants according to patient's HPO terms



(Robinson et. al, 2014)

Results section

Use Exomiser (IRDiRC recognised resource) to prioritise variants according to patient's HPO terms

Phenotypes

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Exomiser will run with the following HPO terms:

HP:0003128 HP:0010964 HP:0200125 HP:0003535 HP:0003344 HP:0004359 HP:0000252 HP:0000488
HP:0001250 HP:0001290 HP:0001644 HP:0002361 HP:0003198 HP:0010531

SUBMIT

RESULTS

PROM1

Exomiser Score: 0.605

Phenotype matches:

PhenIX semantic similarity score: 2.61 (p-value: 0.002410)

Known diseases:

OMIM:603786 Stargardt disease 4 - autosomal dominant
OMIM:608051 Macular dystrophy, retinal, 2 - autosomal dominant
OMIM:612095 Retinitis pigmentosa 41 - autosomal recessive
OMIM:612657 Cone-rod dystrophy 12 - autosomal dominant
ORPHA:1872 Cone Rod Dystrophy
ORPHA:791 Retinitis Pigmentosa
ORPHA:827 Stargardt Disease


Top ranked variants:

SPLICING


 chr4:g.16037357C>T [0/1] rs777673930 (variation viewer)
Variant score: 0.898 CONTRIBUTING VARIANT

Transcripts:


PROM1:uc003goo.2:c.303+1G>A:p.?
PROM1:uc003gor.2:c.303+1G>A:p.?
PROM1:uc003got.2:c.303+1G>A:p.?
PROM1:uc003gop.2:c.277-2225G>A:p.(=)
PROM1:uc003goq.3:c.277-2225G>A:p.(=)
PROM1:uc003gos.2:c.277-2225G>A:p.(=)
PROM1:uc003gou.2:c.277-2225G>A:p.(=)
PROM1:uc010lec.1:c.-63-2225G>A:p.(=)




EJP RD



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centro nacional de análisis genómico



CRG
Centre for Genomic Regulation



Funded by the
European Union
GA n°825575


Results section

CNV analysis results available

Multiple tabs with detailed information for data interpretation

Annotations

OMIM Phenotype ⁱ	Bayes Factor ⁱ	DGV goldstd overlap ⁱ	DGV goldstd coordinates ⁱ
Metabolic encephalomyopathic crises; recurrent; with rhabdomyolysis; cardiac arrhythmias; and neurodegeneration;	28.6	100,100,100,100,0.00,7.77,0.00	22:19033305-21651007,22:18733650-20256447,22:19678592-20311988,22:20030190-20061688,22:20031029-20031029,22:20031054-20032710,22:20032721-20032721



Phenotype

Analysis status

Variants (35)

CNVs (1)

Exomiser

First

Previous

1

Next

Last

Sample	Chr	Start	End	Length	Type	Gene	Reads observed	Reads expected	Reads ratio ⁱ	Internal frequency	Tool
Case15C	22	20030879	20052185	21306	deletion	AC006547.15 TANGO2 AC006547.13	415	746	0.556	0.004259	ExomeDepth



HANDS ON!

Platform walkthrough

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```
ro@n8 indelcalling]$ awk 'print $1$2' caca.vcf
syntax error
ro@n8 indelcalling]$
```

```
ro@n8: /COPY temp/indelcalling
help! for more information.
scratch/devel/fcastro/data/1000genomes/indelcalling/CEU* .
```

```
O|O:123:123,123 O|O:123:123,123 O|1:123:123,123 O|1:49:52,5
123,123 O|O:123:123,123 O|O:123:123,123 O|O:123:123,123 O|O:52:123,
O|O:123:123,123 O|O:123:123,123 O|O:123:123,123 O|O:123:123,123
123,123 O|1:123:123,123
O|O:123:123,123 1|O:123:123,123:56;0.0852854;21;19 O|O:123:123
O|O:123:123,123 O|O:83:83,123 O|1:43:123,43 O|O:123:123,123 O|O
123,123 1|O:68:68,123 O|O:123:123,123 O|O:123:123,123 O|O
O|O:51:123,51 O|O:43:43,123 O|O:87:123,87 O|O:114:123
123,123 1|O:37:37,123 O|O:123:123,123 O|O:123:123,123 O|O
O|O:123:123,123 1|O:123:123,123
O|O:123:123,123 O|O:123:123,123:59;0.102882;5;3 O|O:113:123
123,123 O|O:123:123,123 O|O:123:123,123 O|O:76:105,76 O|O
O|1:123:123,123 O|O:76:76,123 O|O:123:123,123 O|O:123:123,123
123,123 O|O:123:123,123 O|O:123:123,123 1|O:123:123,123
O|O:123:123,123 1|O:123:123,123 O|1:106:123,106
123,123 O|O:113:123,113
Q1,HQ2 O|O:123:1
```



Case A: description

<https://playground.rd-connect.eu/>



Try out the **Genomics Platform** by exploring 50x WGS data for an Illumina Platinum HapMap trio processed using the RD-Connect standard analysis pipeline.

Background

We have generated several trios (father-mother-child), using the same three HapMap samples (NA12877, NA12878, NA12882), but for each trio we have spiked-in real causative variants. A clinical description of these pseudo-cases is provided to download below:

⬇ [Download phenotypic descriptions](#)

1. Click on [Genome-Phenome Analysis Platform](#) and **Login** with username: **test**, password: **1234**
2. Start by going to "**Filters -> Sample Selection -> Select individual Samples**" and add three samples: the individual samples can be selected by typing in **CaseNF**, **CaseNM**, **CaseNC**, but replacing the "N" with the corresponding numbers shown in the phenotypic descriptions file. For example the first trio is **Case1F** (father), **Case1M** (mother), **Case1C** (child).
3. Once you have entered the **IDs**, scroll down to the bottom of the screen and see the phenotypic description of the case (Mode of inheritance, and HPO terms) in the "**Phenotype**" tab.
4. You can apply more **filters** before running the query to try to find the causative variants. **Video tutorials** are available [here](#).

Login



Genome-Phenome Analysis Platform

Log In

Username

Password

Log In



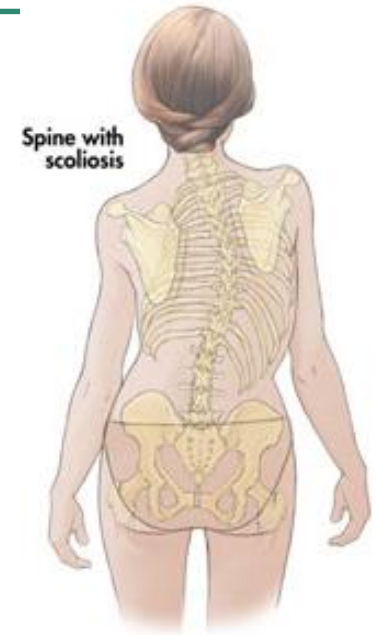
Case A: description

Indication for referral: congenital myasthenic syndrome

(group of conditions characterised by muscle weakness (myasthenia) that worsens with physical exertion)

Case description: 5 years old girl that presented with **progressive motor developmental delay**, **mild muscular weakness** in upper legs, **facial hypotonia** and **skeletal abnormalities** involving curving of the spine. **No cognitive impairment**

Family history: First child and no other relatives affected.





Case A: description

Patient information

Identifier:

Sex:

Global mode of inheritance:

| Sporadic

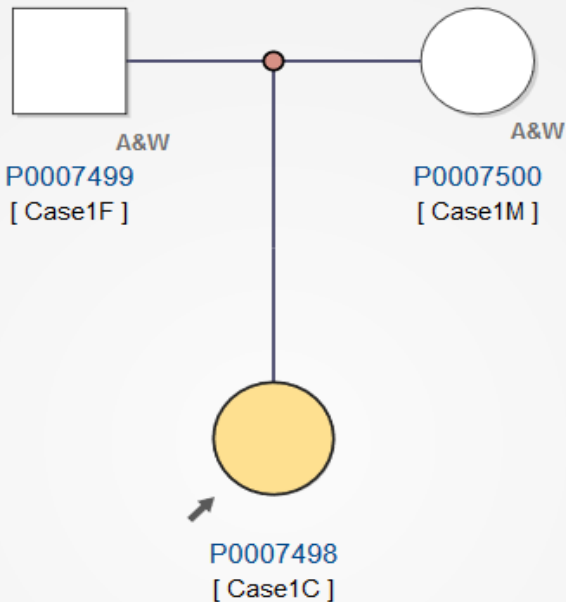
| NO Consanguinity

Global pace of progression:

| Slow progression

Global age of onset:

| Congenital onset



Clinical symptoms and physical findings

MUSCLE BULK

Muscle atrophy
Arthrogryposis multiplex congenita
Distal arthrogryposis

WEAKNESS

Neck

MOTOR ABILITY

Inability to walk

can crawl and stand with KAFOs at 4 yrs

LIMBS

Congenital hip dislocation

IMMUNE SYSTEM

Recurrent lower respiratory tract infections

NERVOUS SYSTEM

NO Intellectual disability

MUSCULATURE

Muscular hypotonia
Neonatal hypotonia
Weakness of facial musculature

- Pedigree editor
- phenotypic information is entered using **HPO**, **OMIM** and **ORDO** ontologies
- **Suspected de novo variant**

Case solving

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```
O|O:123:123,123 O|O:123:123,123 O|1:123:123,123 O|1:49:52,5
123,123 O|O:123:123,123 O|O:123:123,123 O|O:123:123,123 O|O:52:123,
O|O:123:123,123 O|O:123:123,123 O|O:123:123,123 O|O:123:123,123
123,123 O|1:123:123,123
O|O:123:123,123 1|O:123:123,123:56;0.0852854;21;19 O|O:123:123
O|O:123:123,123 O|O:83:83,123 O|1:43:123,43 O|O:123:123,123 O|O:
123,123 1|O:68:68,123 O|O:123:123,123 O|O:123:123,123 O|O:
O|O:51:123,51 O|O:43:43,123 O|O:87:123,87 O|O:114:123
123,123 1|O:37:37,123 O|O:123:123,123 O|O:123:123,123 O|O:
O|O:123:123,123 1|O:123:123,123
O|O:123:123,123 O|O:123:123,123:59;0.102882;5;3 O|O:113:123
123,123 O|O:123:123,123 O|O:123:123,123 O|O:76:105,76 O|O:
O|1:123:123,123 O|O:76:76,123 O|O:123:123,123 O|O:123:123,123
123,123 O|O:123:123,123 O|O:123:123,123 1|O:123:123,123
O|O:123:123,123 1|O:123:123,123 O|1:106:123,106
123,123 O|O:113:123,113
Q1,HQ2 O|O:123:1
```

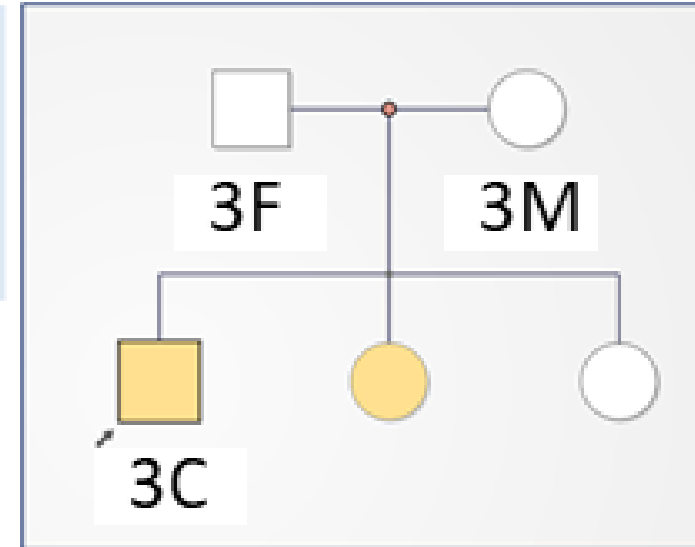
```
ro@n8 indelcalling$ awk 'print $1$2' caca.vcf
syntax error
^ backslash not last character on line
ro@n8 indelcalling$
```

```
ro@n8: /COPY temp/indelcalling
help! for more information.
scratch/devel/fcastro/data/1000genomes/indelcalling/CEU* .
```




Case C: description

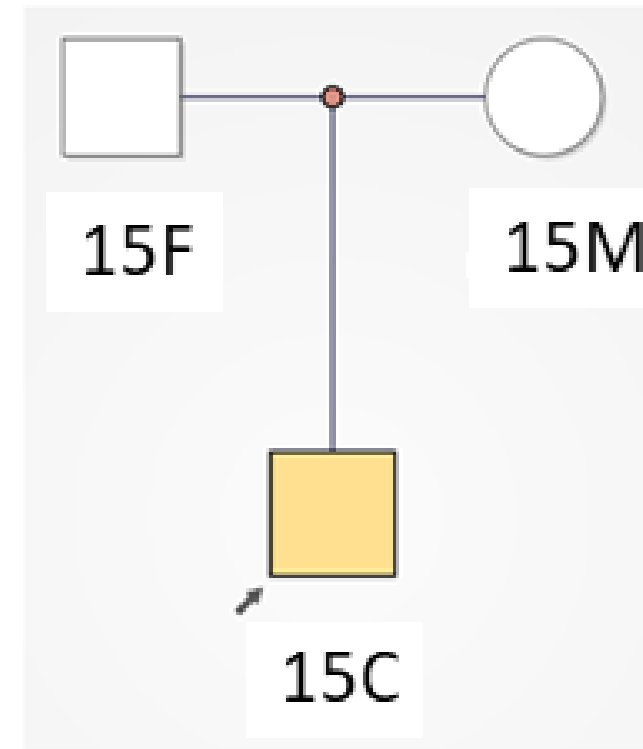
Gender	Male
Age	16 years
Referral	Muscular dystrophy
Onset	Juvenile
Global pace of progression	Progressive
Main clinical features	<ul style="list-style-type: none">• Muscle weakness• Dystrophic muscle biopsy• Quadriceps muscle atrophy• Myalgia





Case D: description

Gender	Male
Age	4 years
Referral	Metabolic diseases with epilepsy
Onset	Infantile onset
Global pace of progression	Progressive
Main clinical features	<ul style="list-style-type: none">• Rhabdomyolysis• Metabolic acidosis• Seizures• Global developmental delay• Ventricular tachycardia



Discussion and demo of other useful features

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```
O|O:123:123,123 O|O:123:123,123 O|1:123:123,123 O|1:49:52,5
123,123 O|O:123:123,123 O|O:123:123,123 O|O:123:123,123 O|O:52:123,
O|O:123:123,123 O|O:123:123,123 O|O:123:123,123 O|O:123:123,123
123,123 O|1:123:123,123
O|O:123:123,123 1|O:123:123,123:56;0.0852854;21;19 O|O:123:123
O|O:123:123,123 O|O:83:83,123 O|1:43:123,43 O|O:123:123,123 O|O
123,123 1|O:68:68,123 O|O:123:123,123 O|O:123:123,123 O|O
O|O:51:123,51 O|O:43:43,123 O|O:87:123,87 O|O:114:123
123,123 1|O:37:37,123 O|O:123:123,123 O|O:123:123,123 O|O
O|O:123:123,123 1|O:123:123,123
O|O:123:123,123 O|O:123:123,123:59;0.102882;5;3 O|O:113:123
123,123 O|O:123:123,123 O|O:123:123,123 O|O:76:105,76 O|O
O|1:123:123,123 O|O:76:76,123 O|O:123:123,123 O|O:123:123
123,123 O|O:123:123,123 O|O:123:123,123 1|O:123:123,123
O|O:123:123,123 1|O:123:123,123 O|1:106:123,106
123,123 O|O:113:123,113
Q1,HQ2 O|O:123:1
```

```
ro@n8 indelcalling] $ awk 'print $1$2' caca.vcf
syntax error
^ backslash not last character on line
ro@n8 indelcalling] $
```

```
ro@n8: /COPY temp/indelcalling
help! for more information.
scratch/devel/fcastro/data/1000genomes/indelcalling/CEU* .
```

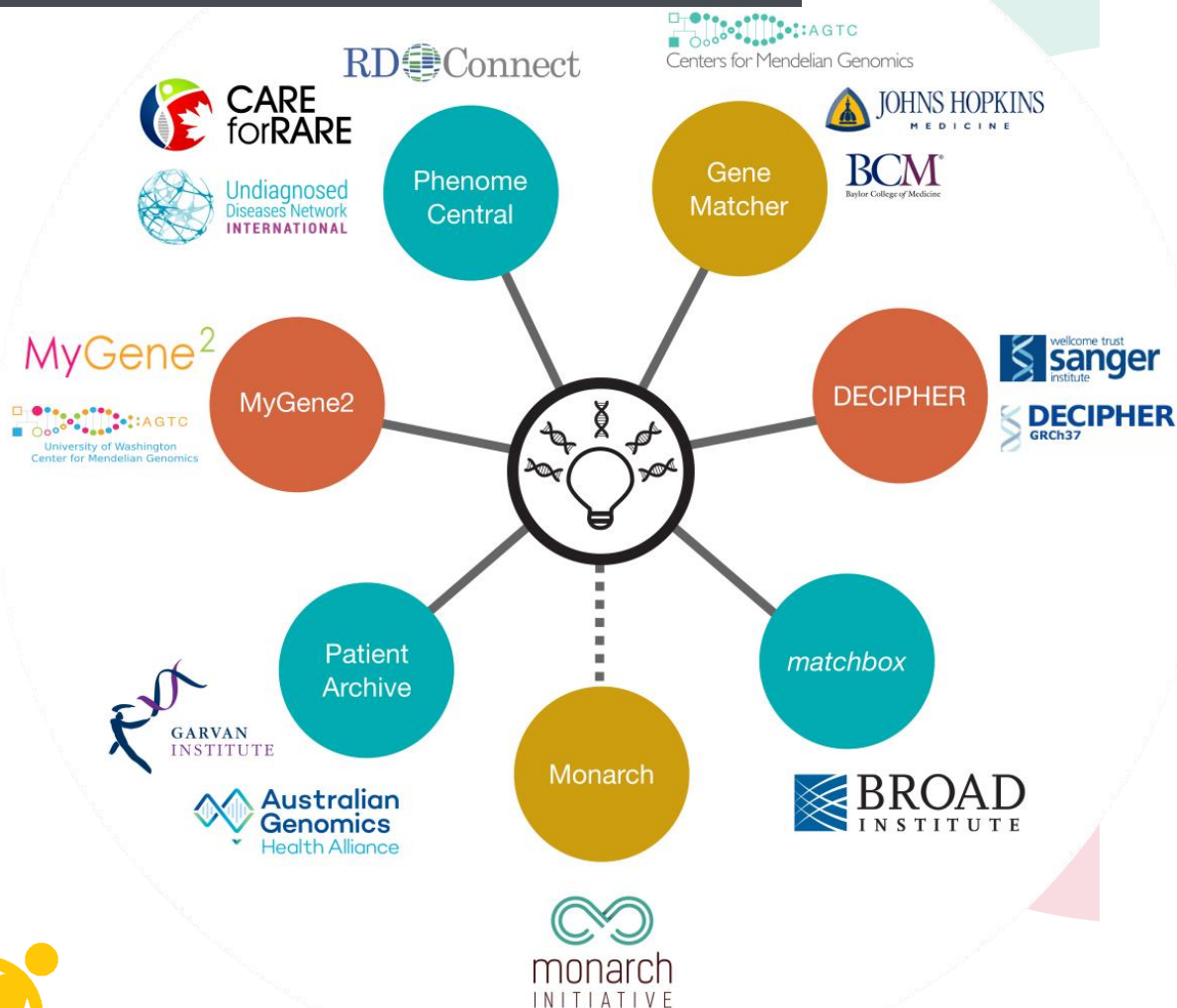
Additional features of interest for data analysis and interpretation



Additional features of interest for data analysis and interpretation

Matchmaker Exchange

Genomic discovery through the exchange of phenotypic & genotypic profiles



Question: Do you have a patient with similar phenotype and genotype as mine?

Data discovery

Question: Do you have a patient with similar phenotype and genotype as mine?

PhenoTips ID

Target Endpoint

Mode of Inheritance **Age of Onset**

Candidate gene(s)

[✕ Remove all](#)

Add gene(s)

HPO term(s) +



Global Alliance
for Genomics & Health
Collaborate. Innovate. Accelerate.



Matches found: 16

Score (0 to 1), is based on a gene-match and a phenotypic similarity which is calculated using the: UI
score

Contact	Patient	Score	Submitter	Phenotype	Genes
CONTACT	<input type="text"/>	0.72	RD-Connect Matchmaker Exchange	Muscle fiber atrophy ,Abnormality of muscle morphology ,Chewing difficulties ,Abnormality of muscle fibers ,Episodic flaccid weakness ,Proximal muscle weakness ,Type 2 muscle fiber atrophy ,EMG: decre...	CHRND
CONTACT	<input type="text"/>	0.70	RD-Connect Matchmaker Exchange	Fatigable weakness ,EMG: decremental response of compound muscle action potential to repetitive nerve stimulation ,Ptosis ...	CHRND

Contact us!

If you ...

- ✓ ... would like to submit data to the RD-Connect GPAP
- ✓ ... are interested in piloting a local RD-Connect GPAP instance
- ✓ ... have questions or would like to explore collaborations

Visit platform.rd-connect.eu
email platform@rd-connect.eu



@ConnectRD

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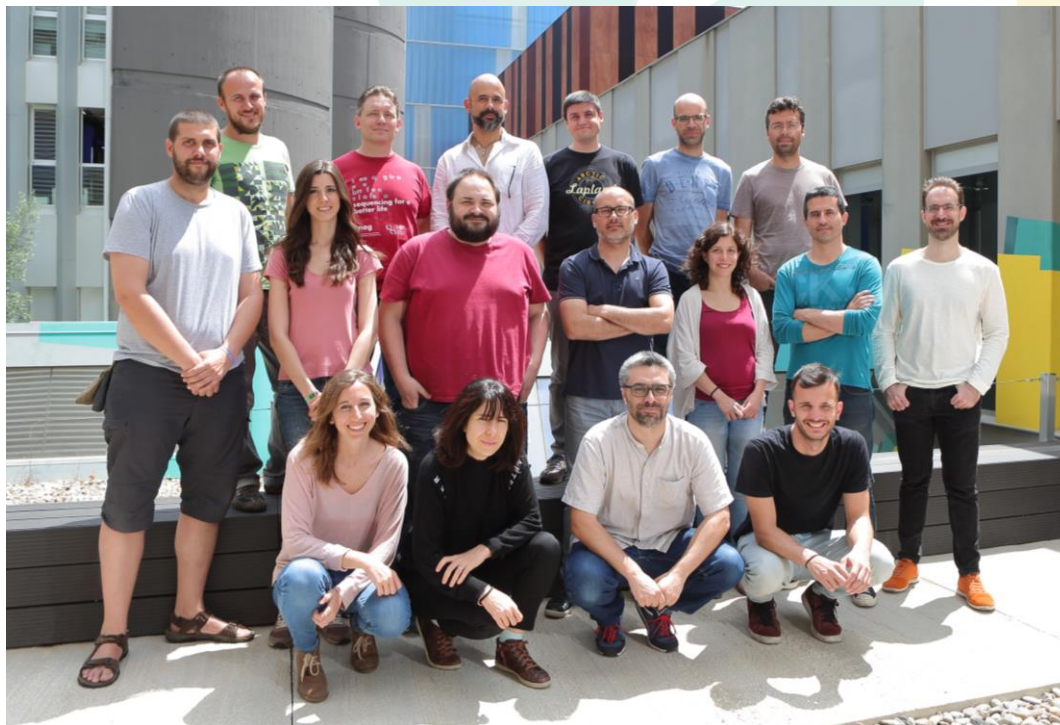
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centro nacional de análisis genómico



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European Union
GA n°825575

Acknowledgments

Bioinformatics Analysis Unit



Data analysis: S. Beltran, R. Tonda, J.R. Trotta, G. Parra, J. Morata, S. Laurie, L. Matalonga, G. Bullich, I. Paramonov, D. Piscia, A. Papakonstantinou, D. Picó, M. Fernández, A. Corvo, C. Garcia, C. Hernández

Production Bioinformatics: M. Ingham, J. Camps, E. Casals, E. Marmesat

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