



IRDiRC

INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

Advancing Rare Disease Research through International Collaboration: IRDiRC

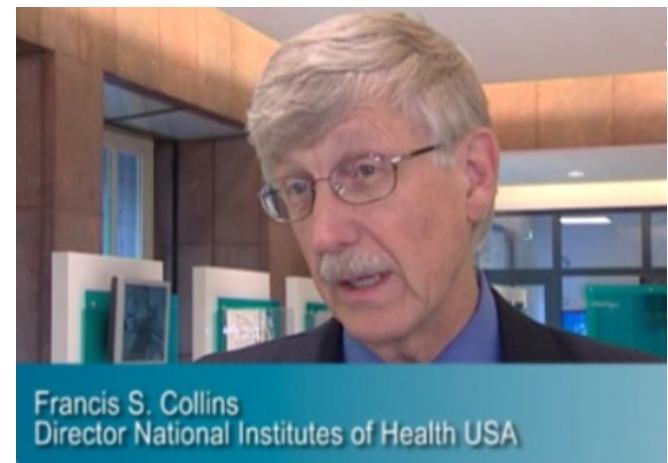
Kym Boycott, Clinician Investigator

Children's Hospital of Eastern Ontario
University of Ottawa, Canada

Co-Chair, Diagnostics Committee, IRDiRC

The idea - 2009.....

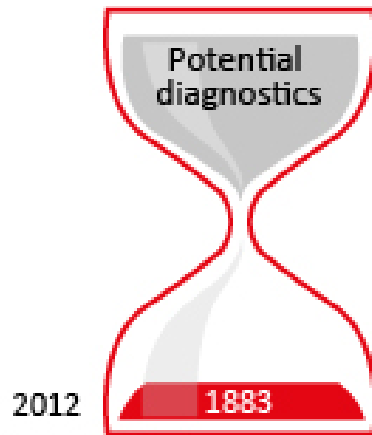
Improved international collaboration and coordination could better facilitate research and could reduce inequities for patients.





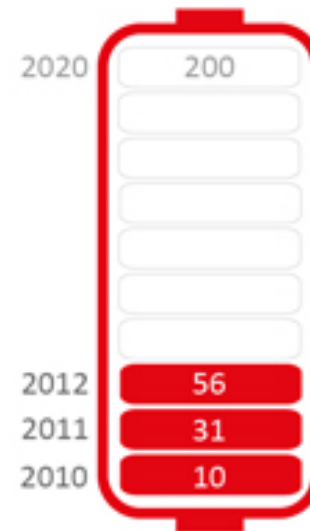
IRDiRC—Ambitious Goals

NEW DIAGNOSTICS



Objective 2020: diagnostics for all rare diseases

NEW THERAPIES



Objective 2020: 200 new therapies

Published online 4 April 2011 | *Nature* **472**, 17 (2011) | doi:10.1038/472017a

News

Rare-disease project has global ambitions



IRDIRC

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Australia

- Western Australian Department of Health



Canada

- Canadian Institutes for Health Research
- Genome Canada



China

- Beijing Genomics Institute
- Chinese Rare Disease Research Consortium



EU

- European Commission



Finland

- Academy of Finland



France

- French Association against Myopathies
- Agence National de la Recherche
- Lysogene



Georgia

- Children's New Hospital Management Group



Germany

- Federal Ministry of Education and Research



Italy

- Italian Higher Institute of Health
- Telethon Foundation



International Consortium

- E-RARE 2 Consortium



Netherlands

- The Netherlands Organization for Health Research and Development



Republic of Korea

- Prosensa
- Korean National Institute of Health



Spain

- National Institute of Health Carlos III



UK

- National Institute for Health Research

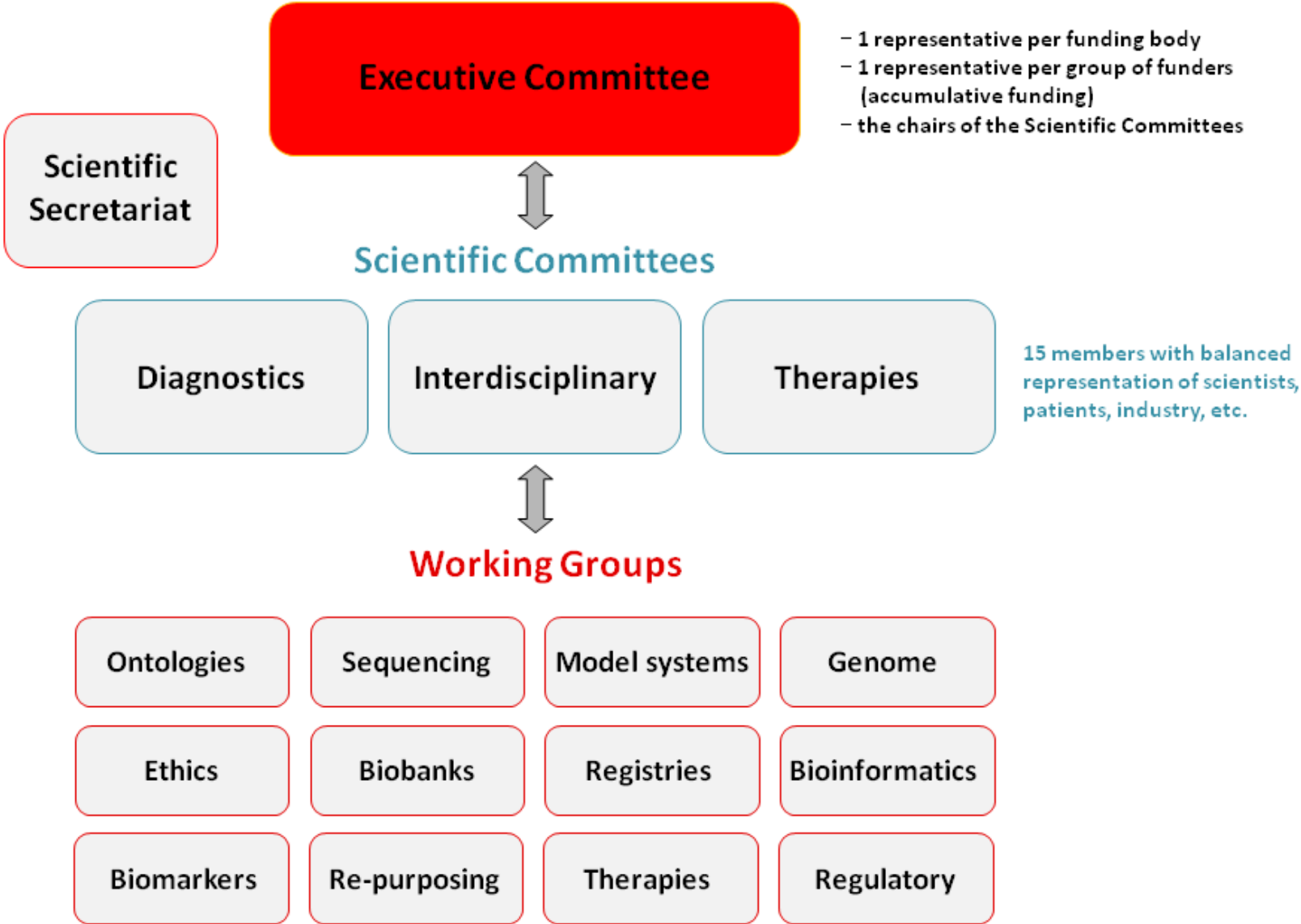


USA

- Food and Drug Administration Orphan Products Grants Program
- National Human Genome Research Institute (NIH)
- National Center for Advancing Translational Sciences(NIH)
- National Cancer Institute (NIH)
- National Eye Institute (NIH)
- National Institute of Neurological Disorders and Stroke (NIH)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH)
- National Institute of Child Health and Human Development (NIH)
- National Eye Institute (NIH)
- NKT Therapeutics
- Office of Rare Diseases (NIH)
- PTC Therapeutics
- Sanford Research Institute
- Shire

Present commitment exceeds \$1B worldwide

IRDiRC Organizational Structure





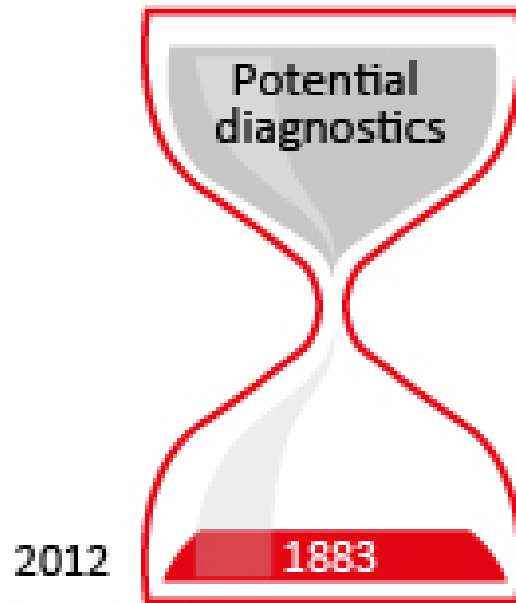
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Diagnostics Scientific Committee

NEW DIAGNOSTICS

No. of new causative genes discovered



1. Understand the mechanism of most RD by 2020
2. Enable the clinical translation of genomic sequencing for patients with RDs

Objective 2020: diagnostics for all rare diseases



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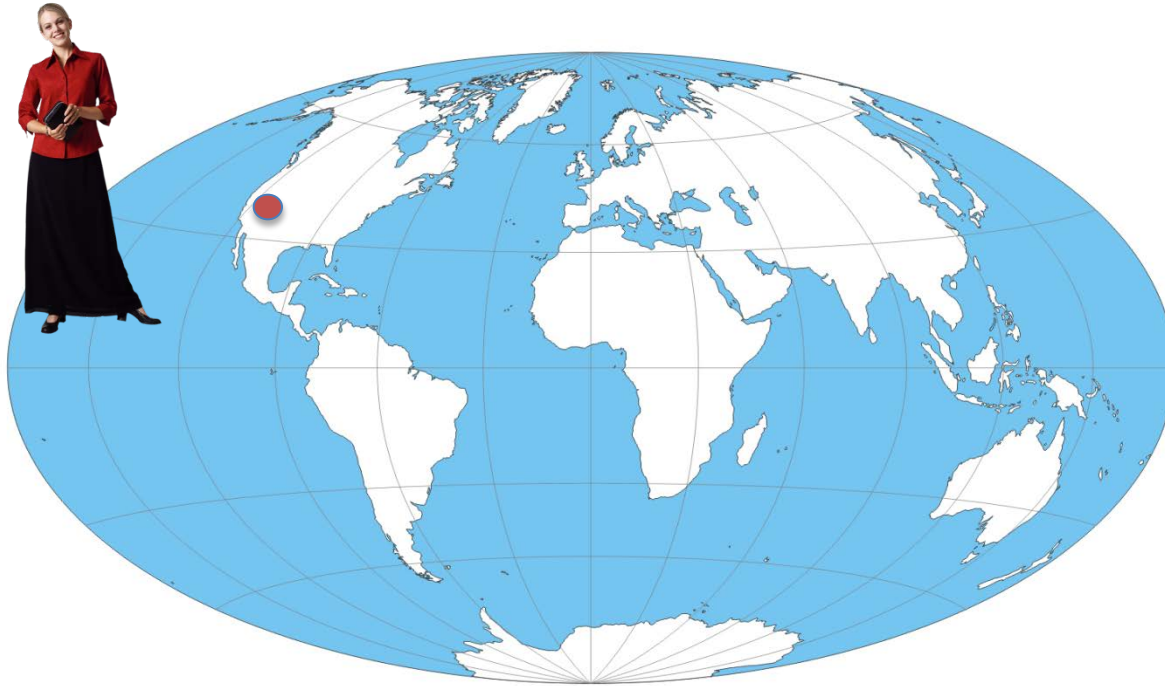
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The Challenge

- ~75% of exome sequencing cases unsolved
- No unified database exists for patients with unsolved rare genetic disease
- Phenotypic data is under-represented in most genomic datasets

Challenge: N-of-1

Patient #1
Clinical Geneticist #1



**Phenotypic
Data**

Feature 1
Feature 2
Feature 3
Feature 4
Feature 5

Genotypic Data

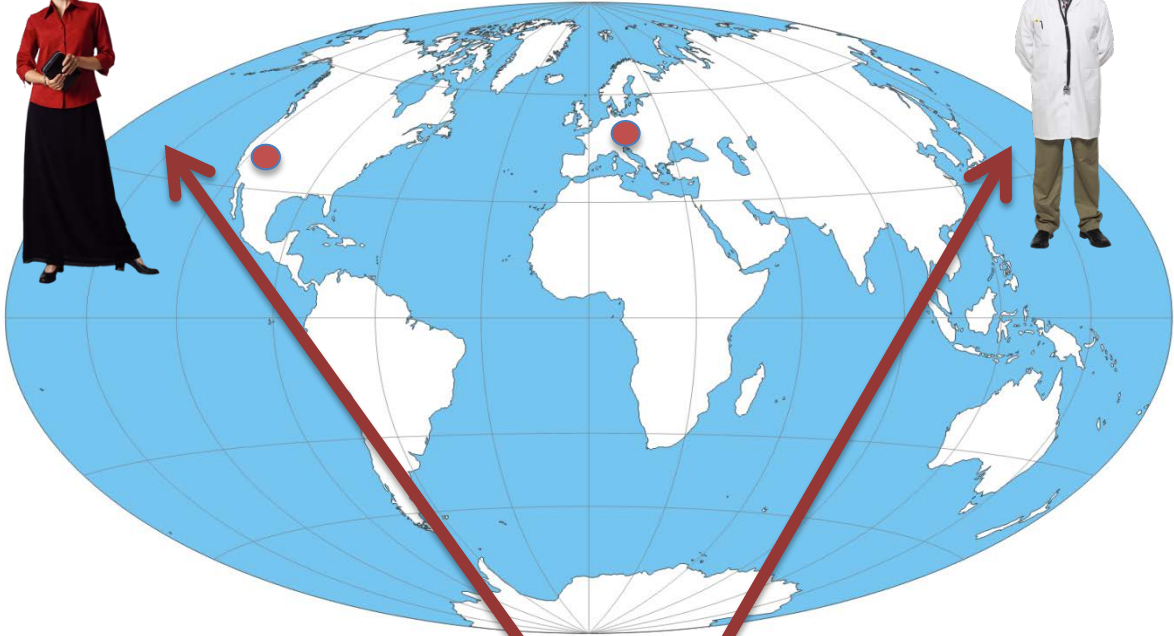
Gene A
Gene B
Gene C
Gene D
Gene E
Gene F

Challenge: N-of-1

Patient #1
Clinical Geneticist #1



Patient #2
Clinical Geneticist #2



Phenotypic Data

- Feature 1
- Feature 2
- Feature 3
- Feature 4
- Feature 5

Genotypic Data

- Gene A
- Gene B
- Gene C
- Gene D
- Gene E
- Gene F

Genomic Matchmaker

Genotypic Data

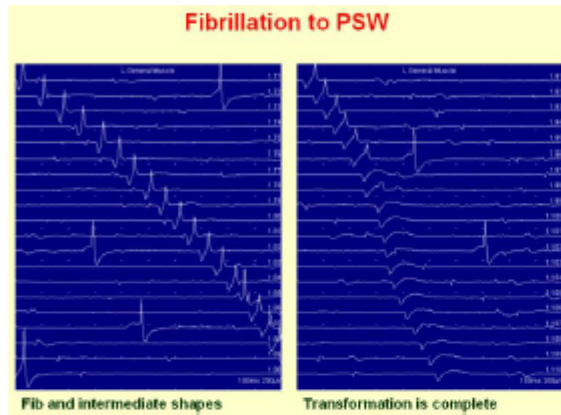
- Gene D
- Gene G
- Gene H

Phenotypic Data

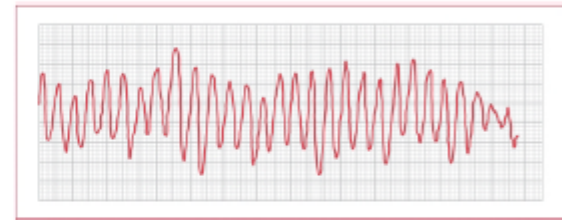
- Feature 1
- Feature 3
- Feature 4
- Feature 5
- Feature 6

Describing the Phenotype

Why Ontologies?



fibrillation . . .



fibrillation . . .

muscle fibrillation = fibrillation \neq fibrillation = ventricular fibrillation

- Need to make sure each term is well defined

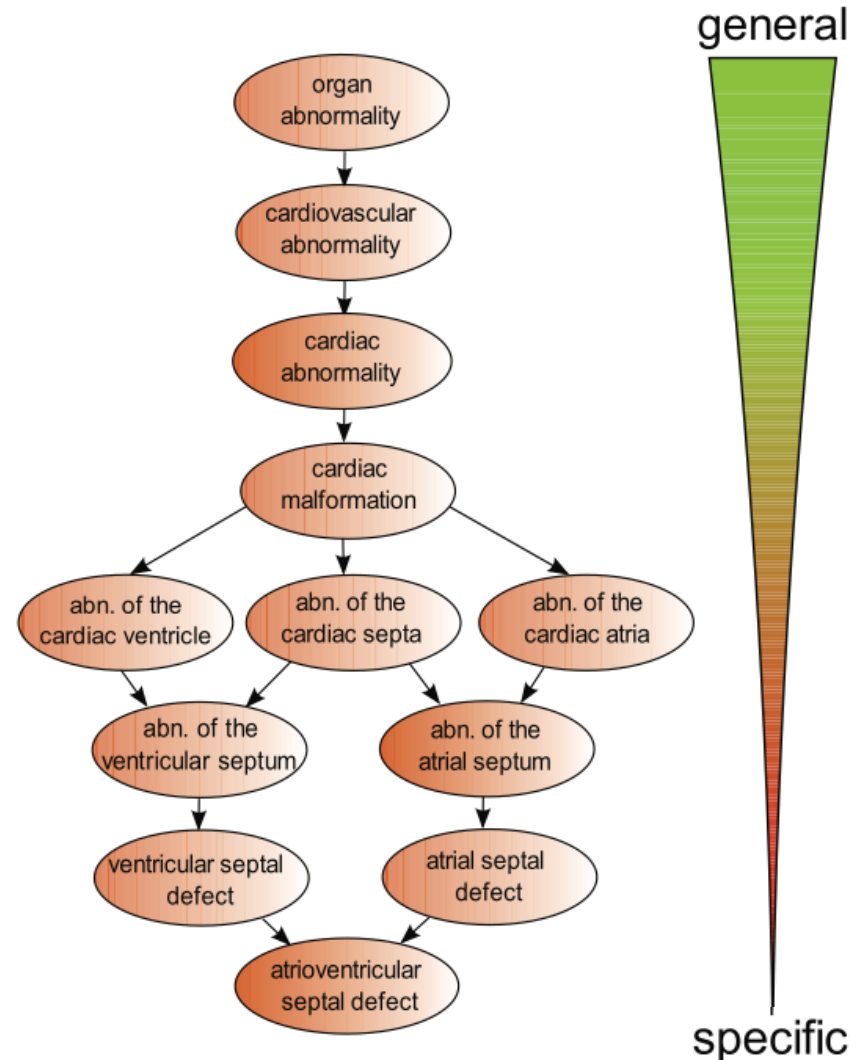
Ontologies

Standardized vocabulary to describe clinical phenotypes

Computer readable terms

Hierarchical structure representing subclass relationships

Human Phenotype Ontology

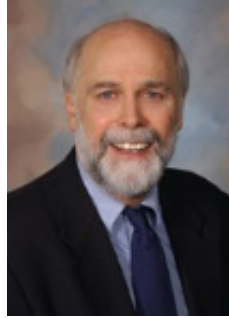




2300 Standard Terms for RD

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Human Phenotype Ontology

Orphanet

LDDDB

Elements of Morphology

PhenoDB

UMLS

SNOWMEDCT

MeSH

MedDRA



International Consortium of Phenotype Terminologies

Matchmaker Needed



PhenomeCentral

An integrated portal for sharing and searching patient phenotype data for rare genetic disorders

» PhenomeCentral

PhenomeCentral

ABOUT

[READ MORE »](#)

PhenomeCentral is an integrated portal for sharing and searching patient phenotype data for rare genetic disorders. It aims to provide a centralized repository for difficult genetic disorder cases, enabling discovery and collaboration while preserving patient privacy.

PARTICIPATING CONSORTIA

[READ MORE »](#)



Care for Rare
40 members
109 contributions



The NIH Undiagnosed Diseases Program (UDP)
2 members
25 contributions

MY DATA

[+ NEW PATIENT RECORD](#)

Results 1 - 6 out of 6 per page of 25

Page 1

Report name	Reported by	Report date	Identifier
<input type="text" value="Type to filter..."/>	<input type="text" value="Type to filter..."/>		<input type="text" value="Type to filter..."/>
P0000159	Taila Hartley	2013/11/25 14:08	165_10-4099
P0000160	Taila Hartley	2013/11/25 15:18	411_G0091AG
P0000161	Taila Hartley	2013/11/25 15:25	411_G0071AG
P0000162	Taila Hartley	2013/11/25 15:41	165_11-151
P0000163	Taila Hartley	2013/11/25 15:56	165_15664
P0000164	Taila Hartley	2013/11/25 16:07	165_120729W

Page 1

DATA SHARED WITH ME

Results 1 - 25 out of 109 per page of 25

Page 1 2 3 4 5

Report name	Reported by	Report date	Identifier
<input type="text" value="Type to filter..."/>	<input type="text" value="Type to filter..."/>		<input type="text" value="Type to filter..."/>
E0000000	Marta Girdea (admin)	2013/09/29 18:10	KR_174_81272



www.phenomecentral.org

Dr. Mike Brudno
U of T

Step 1: Add Patient

- Predictive Search: allowing rapid entry with Human Phenotype Ontology (HPO) terms
- Selection of positive and negative terms
- Add a vcf file (or list of genes)
- Set each record as Private, Public or **Matchable**

Patient information Hide

Identifier:

Date of birth: 02/27/2014 📅

Sex: Male Female

Indication for referral:

Family history Show

Prenatal and perinatal history Show

Medical history Show

Measurements Show

Clinical symptoms and physical findings Hide

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

▼ 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)

▼ CRANIOFACIAL

▶ NA Y N Craniosynostosis

▶ NA Y N Cleft upper lip

▶ NA Y N Cleft palate

▶ NA Y N Abnormal facial shape

Other

CURRENT SELECTION

CRANIOFACIAL

Craniosynostosis Delete - Add details

EYE DEFECTS

Coloboma Delete - Add details

NO Cataract Delete - Add details

▼ YOU MAY WANT TO INVESTIGATE...

Phenotypes that are likely to help improve differential diagnosis

<input type="checkbox"/> Y <input type="checkbox"/> N Bruising susceptibility	<input type="checkbox"/> Y <input type="checkbox"/> N degeneration
<input type="checkbox"/> Y <input type="checkbox"/> N Progressive sensorineural hearing impairment	<input type="checkbox"/> Y <input type="checkbox"/> N Sparse eyebrow
<input type="checkbox"/> Y <input type="checkbox"/> N Prolonged bleeding time	<input type="checkbox"/> Y <input type="checkbox"/> N Aortic valve stenosis
<input type="checkbox"/> Y <input type="checkbox"/> N Giant platelets	<input type="checkbox"/> Y <input type="checkbox"/> N Fat malabsorption
<input type="checkbox"/> Y <input type="checkbox"/> N Abnormality of the urinary system	<input type="checkbox"/> Y <input type="checkbox"/> N Calcific mitral valve stenosis
<input type="checkbox"/> Y <input type="checkbox"/> N Abnormal bleeding	<input type="checkbox"/> Y <input type="checkbox"/> N Aortic valve calcification
<input type="checkbox"/> Y <input type="checkbox"/> N Excessive wrinkling of palmar skin	<input type="checkbox"/> Y <input type="checkbox"/> N Early progressive calcific cardiac valvular disease
<input type="checkbox"/> Y <input type="checkbox"/> N Polyarticular arthropathy	<input type="checkbox"/> Y <input type="checkbox"/> N Multiple palmar creases
<input type="checkbox"/> Y <input type="checkbox"/> N Mitral valve prolapse	<input type="checkbox"/> Y <input type="checkbox"/> N Deep philtrum
<input type="checkbox"/> Y <input type="checkbox"/> N Myxomatous mitral valve	<input type="checkbox"/> Y <input type="checkbox"/> N Camptodactyly (feet)
	<input type="checkbox"/> Y <input type="checkbox"/> N Large eyes

Step 2: See Patients Similar To Yours

F0000010 Reported by **Marta Girdea (admin)** on 2013/09/29 18:10 · Last modified by **Marta Girdea** on 2013/09/30 14:00

This case is owned by **Care4Rare**, it is **public**, and it is shared with **1 collaborator**

Patient information

Identifier: KB_174_FHS1-1
Sex: Female

Clinical symptoms and physical findings

CRANIOFACIAL
 Low hanging columella
 Thin upper lip vermillion
 Short philtrum
 Triangular face
 Wide nose
 Prominent nasal tip
 Narrow nasal bridge
 Long nose
 NO Wide mouth

EAR DEFECTS
 Low-set ears
 Recurrent otitis media

MUSCULOSKELETAL
 Broad fingertip
 Brachydactyly syndrome
 Broad thumb

GENITOURINARY
 Nephrocalcinosis
 Hydronephrosis

BEHAVIOR, COGNITION AND DEVELOPMENT
 Moderate expressive language delay

GENE MATCHING BREAKDOWN

SRCAP

HIDE VARIANTS...

Estimated relevance for the observed phenotype in the **current patient**: ■■■□□ 60%

Estimated relevance for the observed phenotype in the **other patient**: ■■■□□ 65%

VARIANT	ESTIMATED HARMFULNESS
chr16:30748691-30748691 C → T (STOPGAIN)	■■■■■ 95%
chr16:30697203-30697203 G → C (NONSYNONYMOUS)	■■■□□ 57%

VARIANT	ESTIMATED HARMFULNESS
chr16:30751917-30751917 G → A (FS_INSERTION)	■■■■■ 95%

FOXO3

Estimated relevance for the observed phenotype in the **current patient**: ■■■□□ 57%

Estimated relevance for the observed phenotype in the **other patient**: ■■□□□ 50%

Diagnosis

OMIM disorder: #136140 FLOATING-HARBOR SYNDROME; FLHS

Similar cases available in the database

Showing 10 similar cases REFRESH

Case ID	Diagnosis	Relevance	Details
F0000021	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■■□	Matches found for 14 out of 17 features. Show matches...
F0000019	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■■□	Matches found for 14 out of 17 features. Show matches...
F0000012	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■■□	Matches found for 14 out of 17 features. Show matches...
F0000009	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■■□	Matches found for 14 out of 17 features. Show matches...
F0000011	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■■□	Matches found for 14 out of 17 features. Show matches...
F0000020	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■■□	Matches found for 14 out of 17 features. Show matches...
F0000014	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 13 out of 17 features. Show matches...
F0000017	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 13 out of 17 features. Show matches...
F0000016	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 11 out of 17 features. Show matches...
F0000015	#136140 FLOATING-HARBOR SYNDROME; FLHS	■■■□□	Matches found for 14 out of 17 features. Show matches...



ClinVar
&
ClinGenDB

PhenoDB
Gene
Matcher

DECIPHER



Multiple disconnected solutions

LOVD



GEM.app

Phenome
Central

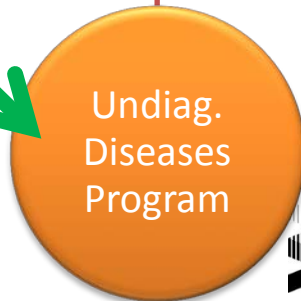
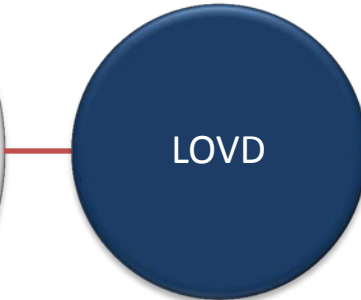
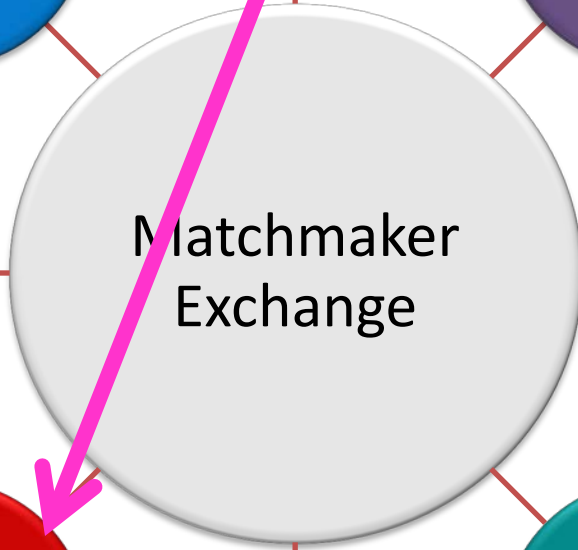
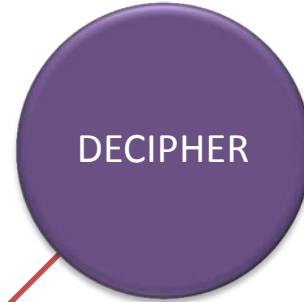
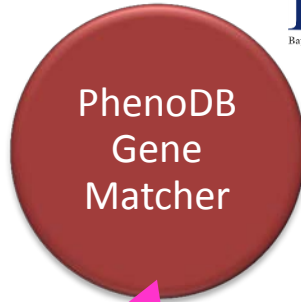
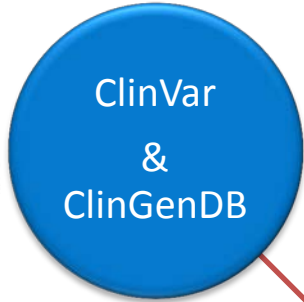


Undiag.
Diseases
Program



Café
Variome





Courtesy of Heidi Rehm



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2nd IRDiRC Conference 7-9 November 2014 - Shenzhen, China

SAVE THE

Access the IRDiRC Conference

