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
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
<table>
<thead>
<tr>
<th>Country</th>
<th>Organizations</th>
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<tbody>
<tr>
<td>Australia</td>
<td>Western Australian Department of Health</td>
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<td>Canada</td>
<td>Canadian Institutes for Health Research</td>
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<td>Genome Canada</td>
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<td>China</td>
<td>Beijing Genomics Institute</td>
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<td>Chinese Rare Disease Research Consortium</td>
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<td>EU</td>
<td>European Commission</td>
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<td>Academy of Finland</td>
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<td>France</td>
<td>French Association against Myopathies</td>
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<td>Agence National de la Recherche</td>
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<td>Lysogene</td>
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<td>Georgia</td>
<td>Children’s New Hospital Management Group</td>
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<td>Germany</td>
<td>Federal Ministry of Education and Research</td>
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<td>Italian Higher Institute of Health</td>
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<td>International Consortium</td>
<td>E-RARE 2 Consortium</td>
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<td>The Netherlands Organization for Health Research and Development</td>
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<td>Proensa</td>
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<td>National Institute of Health Carlos III</td>
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<td>UK</td>
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<td>USA</td>
<td>Food and Drug Administration Orphan Products Grants Program</td>
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<td>National Human Genome Research Institute (NIH)</td>
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<td>National Center for Advancing Translational Sciences(NIH)</td>
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<td>National Cancer Institute (NIH)</td>
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<td>National Eye Institute (NIH)</td>
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<td>National Institute of Neurological Disorders and Stroke (NIH)</td>
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<td>National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH)</td>
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<td>National Institute of Child Health and Human Development (NIH)</td>
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<td>NKT Therapeutics</td>
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<td>Office of Rare Diseases (NIH)</td>
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<td>PTC Therapeutics</td>
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<td>Sanford Research Institute</td>
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Present commitment exceeds $1B worldwide
Diagnostics Scientific Committee

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
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

<table>
<thead>
<tr>
<th>Phenotypic Data</th>
<th>Genotypic Data</th>
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<tbody>
<tr>
<td><strong>Feature 1</strong></td>
<td>Gene A</td>
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<tr>
<td>Feature 2</td>
<td>Gene B</td>
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<tr>
<td><strong>Feature 3</strong></td>
<td><strong>Gene D</strong></td>
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<td>Feature 4</td>
<td>Gene E</td>
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<tr>
<td>Feature 5</td>
<td>Gene F</td>
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</tbody>
</table>
Challenge: N-of-1

Patient #1
Clinical Geneticist #1

Patient #2
Clinical Geneticist #2

Genotypic Data
Gene A
Gene B
Gene C
Gene D
Gene E
Gene F

Phenotypic Data
Feature 1
Feature 2
Feature 3
Feature 4
Feature 5

Gene G
Gene H

Genotypic Data
Gene D

Genomic Matchmaker

Phenotypic Data
Feature 1
Feature 3
Feature 4
Feature 5
Feature 6

Courtesy of Joel Krier
Describing the Phenotype

Why Ontologies?

fibrillation...

fibrillation...

muscle fibrillation ≠ fibrillation ≠ fibrillation = ventricular fibrillation

- Need to make sure each term is well defined

Peter Robinson et al.
Ontologies

Standardized vocabulary to describe clinical phenotypes

Computer readable terms

Hierarchichal structure representing subclass relationships

Human Phenotype Ontology

Robinson, PN and Mundlos, S. 2010
2300 Standard Terms for RD

Human Phenotype Ontology
Orphanet
LDDB
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

About
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

Care for Rare
40 members
109 contributions

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

My Data

Results 1 - 6 out of 6 per page of 25

Report name
Reported by
Report date
Identifier

Type to filter
Type to filter
Type to filter

P0000159
Taila Hartley
2013/11/25 14:08
165_10-4099

P0000160
Taila Hartley
2013/11/25 15:18
411_G0091AG

P0000181
Taila Hartley
2013/11/25 15:26
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 16:09
165_120729W

Data Shared With Me

Results 1 - 25 out of 109 per page of 25

Report name
Reported by
Report date
Identifier

Type to filter
Type to filter
Type to filter

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
Step 2: See Patients Similar To Yours
Step 3: Contact the Submitter of the Other Dataset
Multiple disconnected solutions

- ClinVar & ClinGenDB
- GEM.app
- PhenoDB Gene Matcher
- DECIPHER
- LOVD
- Phenome Central
- Café Variome
- Undiag. Diseases Program

Courtesy of Heidi Rehm
2nd IRDiRC Conference
7-9 November 2014 - Shenzhen, China

Access the IRDiRC Conference