FORGE Canada:
A nation-wide effort to identify genes for rare childhood disorders

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In Canada

~250,000 Canadian children have a rare genetic disease
How many human single gene disorders remain to be discovered?

- Gene known: ~3700
- Gene unknown: ~3300
- Suspected single gene disorders: ??

Depth of Rare Disease

??
7000 rare diseases
FORGE Canada Consortium

Disorders to Study

Core Element Consent

Gene Discovery

Knowledge Translation

National Data Coordination

Guidelines for Return of Incidental Findings

2 year project
April 2011 to June 2013
Finding Of Rare Disease GEnes
What disorders do we study?

>400 Diseases Proposed

>200 Diseases Selected for Study

- Congenital or develops in childhood or adolescence
- Disorder is likely monogenic and gene unknown
- At least one Canadian patient with condition available for study
- Appropriate investigations have been performed to exclude known causes
3 Strategies

Unrelated patients with same disorder

Unrelated families with same disorder

Multiple Alleles

Consanguineous families

AD families with multiple affected members

Mapping Data

Autosomal Recessive disorders

Affected sibpairs

Compound Heterozygous
184 disorders into pipeline ...

Multiple alleles

Mapping data

Compound heterozygous

3 Strategies

gene known

gene unknown
Next-gen phenotyping

<table>
<thead>
<tr>
<th>Patient Information</th>
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<tbody>
<tr>
<td>Identifier:</td>
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<tr>
<td>Patient name:</td>
</tr>
<tr>
<td>Local name:</td>
</tr>
<tr>
<td>Date of birth:</td>
</tr>
<tr>
<td>Sex:</td>
</tr>
<tr>
<td>☐ Male ☐ Female</td>
</tr>
<tr>
<td>Family study:</td>
</tr>
<tr>
<td>☐ Mother ☐ Father ☐ Sibling of</td>
</tr>
<tr>
<td>Patient (MRN):</td>
</tr>
<tr>
<td>Onset:</td>
</tr>
<tr>
<td>☐ Congenital ☐ Specify age</td>
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<tr>
<td>Indication for referral:</td>
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<thead>
<tr>
<th>Prenatal and Perinatal History</th>
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<th>Medical and developmental history</th>
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<th>Measurements</th>
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<tr>
<th>Clinical symptoms &amp; physical findings</th>
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<th>Diagnosis</th>
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<th>Additional files</th>
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Next-gen phenotyping

QUICK PHENOTYPE SEARCH:

Related terms

- Abnormality of the central nervous system
- Seizures
- Dileptic seizures
- Epileptic spasms
- Febrile seizures
- Complex febrile seizures
- Simple febrile seizures
- Focal seizures
- Generalized seizures
- Absence seizures
- Atonic seizures
- Generalized clonic seizures
- Generalized myoclonic seizures
- Generalized tonic seizures
- Generalized tonic-clonic seizures
- Hypotonic seizures
- Hypertonic seizures
- Status epilepticus
- Symptomatic seizures
- Seizures occur in clusters
- Intractable seizures
- Fetal seizure
- Staring episodes during seizures
- Apnea during seizure spells

siezur

- Apnea during seizure spells
- Fetal seizure
- Seizures
- Generalized tonic-clonic seizures
- Focal seizures without impairment of consciousness or awareness
- Bilateral convulsive seizures
- Focal seizures with impairment of consciousness or awareness
- Generalized tonic seizures
- Photomyoclonic seizures
- Simple partial occipital seizures
Data generation and analysis

STICs - exome sequencing -

Project Teams - validation studies -

National Data Coordination Centre
Unrelated patients with same disorder

Strategy – 1 – Multiple Alleles

OMIM 610536: Mandibulofacial dysostosis with microcephaly

Lines et al., AJHG 2012;90: 369
Strategy 1 – Multiple Alleles

- Hajdu-Cheney syndrome
- Chudley McCullough syndrome

- Acrodysostosis*
- Leber Congenital Amaurosis
- Floating Harbor syndrome
- French Canadian Joubert syndrome (2)
- Megalencephaly Capillary Malformation
- Nager syndrome
- Microcephaly Capillary Malformation
- Mandibulofacial dysostosis with Microcephaly
- Weaver syndrome

- 75% success rate
Strategy – 2 - Mapping

<table>
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<tr>
<th>Coding Variants</th>
<th>CASS</th>
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<tbody>
<tr>
<td>Rare variants not in dbSNP</td>
<td>476</td>
</tr>
<tr>
<td>Rare variants not in 160 internal controls</td>
<td>269</td>
</tr>
<tr>
<td>Found in homozygous region</td>
<td>1</td>
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<td>Gene</td>
<td>ZIP8</td>
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ZIP8
SLC39A8
Strategy 2 – Mapping

- **Dominant disorders**
  - 45% success
  - 50% known genes
  - 50% novel genes

- **Recessive disorders**
  - 70% success
  - 60% known genes
  - 40% novel genes
Strategy – 3 - Sibpairs

Nonconsanguineous families – AR disorder

Genes with missense, nonsense, indel or splice variants 6453
Genes with rare mutations * 372
Genes with mutations shared by sibs 109
Genes with homozygous/ multiple heterozygous variants 2

New subtype D-bifunctional protein deficiency

http://www.ottawacitizen.com/technology
December 4, 2011
Strategy 3 – Sibpairs

- 60% success
  - 80% known gene
  - 20% novel genes

Autosomal Recessive
One Gene per Week

184 Disorders

60% solved

40% unsolved

45% novel
5% mechanism
50% diagnosis

1/3 no plausible variants
2/3 too many variants

April 2011 – March 2013
Insights into Depth of Rare Disease

- 1/3 novel genes
- 1/3 diagnosis in known disease gene
  - Atypical phenotypes
  - Conflation of 2 diseases
  - New mechanisms
- 1/3 need more work

the rule of 1/3
180 novel genes identified using WES
International Collaboration

NEW DIAGNOSTICS

Objective 2020: diagnostics for all rare diseases
FORGE to CARE for RARE

Canadian Patients with Rare Diseases

- Expand Human Mutation Atlas
- Clinical Exome Workflow
- Therapeutic Opportunities
Steering Committee

- **Clinical Coordinator**
- **Project Manager**
- **FORGE Membership**
- **International Collaborators**

Francois Bernier  
University of Calgary

Mike Brudno  
University of Toronto

Bridget Fernandez  
Memorial University

Bartha Knoppers  
McGill University

Mark Samuels  
Université de Montréal

Steve Scherer  
University of Toronto

Kym Boycott  
University of Ottawa

Jan Friedman  
University of BC

Jacques Michaud  
Université de Montréal

Janet Marcadier  
Chandree Beaulieu