Matchmaker Exchange: Connecting the Matchmakers to Accelerate Gene Discovery

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On behalf of MME Working Group, IRDiRC, and GA4GH
~7000 Rare Diseases

Reliance on animal models
Reliance on *in silico* prediction
Coverage issues
Poor documentation in the literature

N-of-1

Clinical heterogeneity
Familial dominant disorders
Intrafamilial locus heterogeneity
Dominant and recessive mutations may have very different phenotypes
Different alleles may have very different phenotypes

gene known
~4200

~3000 diseases below the surface
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
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

Genotypic Data
Gene D
Gene G
Gene H

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

Genomic Matchmaker

Courtesy of Joel Krier
Step 1: Add Patient via PhenoTips
Step 2: See Patients Similar to Yours
Step 3: Contact Submitter of Other Dataset

Contact a non-public case owner:

1. Configure your message
   - SUBJECT: Interested in one of your non-public cases
   - Information about you:
     - DISCLOSE YOUR NAME
     - DISCLOSE YOUR EMAIL
     - DISCLOSE YOUR MEMBERSHIP TO PHENOMECENTRAL GROUPS
     - INCLUDE DIAGNOSIS INFORMATION
     - INCLUDE A PHENOTYPE SUMMARY

2. Preview your message
   - SUBJECT: [PhenomeCentral] Interested in one of your non-public cases
   - MESSAGE:
     - Hello <undisclosed recipient name>,
     - A PhenomeCentral user is interested in one of your non-public cases: <undisclosed case identifier>. Please see their message below.
     - PhenomeCentral has identified significant similarities between one of your cases and one of mine.
     - My patient is undiagnosed and presents the following phenotypic features:
       - Absent Achilles reflex
       - Anemia
       - Attention deficit hyperactivity disorder
       - Autonomic dysregulation
       - Decreased corneal reflex
       - Delayed fine motor development
       - Delayed gross motor development
       - Generalized hypotonia
       - Intellectual disability, mild
       - Neonatal hypotonia
       - Reduced tendon reflexes
       - Sensory impairment
       - Sensory neuropathy
     - I would like to grant you the rights to view my case and to obtain view access to your case, and to learn your contact information in order to further discuss these abnormalities with you.
     - Regards,
     - Marta Girdea
     - mart@phenotips.org

   - To accept view privileges from this user and to grant them view access to <undisclosed case identifier>, follow this link: <undisclosed URL>

   Best wishes,
   The PhenomeCentral team
GeneMatcher

- Designed to connect via e-mail clinicians/researchers with interest in a gene about which nearly nothing is known because of patients, animal models, etc.
- Only a human gene symbol or ID is required.
- Can also match on OMIM phenotype numbers.
- Matching on phenotypic features is in development.

Courtesy Ada Hamosh, François Schiettecatte, Nara Sobreira
Growth in Number of Genes & Matches in Gene Matcher

Number


Genes
Matches

Courtesy Ada Hamosh, François Schiettecatte, Nara Sobreira
Multiple disconnected projects
Making a Match

Linking multiple databases is not without its challenges...
Gene and Phenotype (HPO)
**API: Query by Example**

**Request**: a (real) patient profile, with phenotype and/or genotype data

**Response**: a list of similar (potentially unclear) patient profiles, with method to contact submitter
Making a Match

2

A

B

1
Making a Match

1. MME API
2. Person A
3. Person B

A → B
B → A

MME API
Making a Match

1. MME API
2. A
3. B
4. 4
5. 5
### Similar cases available in the database

#### REMOTE DATABASES

Remote server: **GeneMatcher**

Showing 3 similar cases

<table>
<thead>
<tr>
<th>Match ID</th>
<th>Diagnosis</th>
<th>Contact</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1198</td>
<td>Unavailable</td>
<td>Austin Larson, University of Colorado Denver</td>
<td>50%</td>
</tr>
</tbody>
</table>

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#### PHENOTYPIC FEATURES BREAKDOWN

**ABNORMALITY OF THE NERVOUS SYSTEM**

<table>
<thead>
<tr>
<th>The current patient (P8000086) presented with:</th>
<th>The matched patient presented with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic fatigue</td>
<td>Abnormality of the nervous system</td>
</tr>
<tr>
<td>Pain</td>
<td>EEG abnormality</td>
</tr>
<tr>
<td></td>
<td>Generalized myoclonic seizures</td>
</tr>
<tr>
<td></td>
<td>Abnormality of the cerebral cortex</td>
</tr>
<tr>
<td></td>
<td>Morphological abnormality of the central nervous system</td>
</tr>
<tr>
<td></td>
<td>Intellectual disability</td>
</tr>
<tr>
<td></td>
<td>Intellectual disability, profound</td>
</tr>
<tr>
<td></td>
<td>Microcephaly</td>
</tr>
<tr>
<td></td>
<td>Pachygyria</td>
</tr>
<tr>
<td></td>
<td>Congenital microcephaly</td>
</tr>
<tr>
<td></td>
<td>Global developmental delay</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Cerebral calcification</td>
</tr>
</tbody>
</table>

**UNMATCHED**

<table>
<thead>
<tr>
<th>The current patient (P8000086) presented with:</th>
<th>The matched patient presented with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketosis</td>
<td>Abnormality of the head</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td></td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td></td>
</tr>
</tbody>
</table>

### GENE MATCHING BREAKDOWN

**LONP1**

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Remote Server: **DECIPHER**

No similar cases found.
MME Pilot

- Test set of 50 solved cases into both databases
  - All come back
- Tested using 45 unsolved cases with flagged candidates in PhenomeCentral
  - 10 gene matches
    - 6 false positives (discordant phenotypes)
    - 2 unresolved
    - 2 potentially significant
Next Steps
Summary

MME has been focused on hypothesis-driven matching
  • Simple matching of unsolved rare disease cases that share a common phenotype and candidate gene

Goal of the MME is to expand the scope of discovery
  • Hypothesis-free to allow matching in the absence of an identified candidate gene