Deeper phenotyping for diagnostics and discovery

Melissa Haendel
7th Annual Big Data in Biomedicine Symposium
October 27th, 2018

bit.ly/melissa-georgetown @ontowanka
How can we meaningfully group patients when each one is an individual?

Phenotypes
Genes
Environment

signs and symptoms, demographics, exposure, diet, traits, etc.
How can we discover disease mechanisms? Identify treatments?

We need to leverage ALL biological knowledge about the relationships, not just those already related to any given disease or domain.
Prevailing clinical diagnostic pipelines leverage only a tiny fraction of the available data. Under-utilized data results in a loss of discriminatory power.
We must expand knowledge of human disease genes using model organisms.

Even inclusion of just five species boosts phenotypic coverage of genes by 60% (23→83%).

Number of human protein-coding genes in HGNC as of April 2018

Help can come from unexpected places, not just traditional models of disease

- Dog retina has area centralis (analogous to human macula) & fovea-like region similar to humans; useful to study naturally occurring cone diseases
- Aged cats are natural models of AD: they form Abeta oligomers, neurofibrillary tangles, and have neuronal loss
- Naked Mole Rats don't get cancer
- Armadillos are a natural host of M. leprae, the myobacterium that causes leprosy (only one besides humans)
- Tree shrews’ glioblastomas are morphologically & genetically similar to humans (& more similar than mouse models)
Crossing the chasm of (phenotypic) despair*

*Chris Chute
How can we help machines understand phenotypes and how they relate to one another?

Palmoplantar hyperkeratosis

I have absolutely no idea what that means
Different communities use different languages

- Palmoplantar hyperkeratosis
- Ulcerated paws
- Thick hand skin

"HandsEBS" by James Heilman, MD - Own work. Licensed under CC BY-SA 3.0 via Commons – https://commons.wikimedia.org/wiki/File:HandsEBS.JPG#/media/File:HandsEBS.JPG
http://www.guinealynx.info/pododermatitis.html
Challenge: Each data source uses their own vocabulary/ontology
Challenge: Each data source uses their own vocabulary/ontology

- ZFA
- MP
- DPO
- WPO
- FB
- OMIA
- VT
- RGD
- MP
- IMPC
- HB
- OMIM
- QTLdb
- HPOA
- EHR
- SNOMED
- LOINC
- ICD
- FYPO
- WPO
- PB
- APO
- SGD
- ZFIN
Decomposition of complex concepts allows interoperability.

Human phenotype

“Palmoplantar hyperkeratosis”

Mouse phenotype

“Ulcerated paws”

Species neutral ontologies, homologous concepts
"Phenotype blast": recalls correct gene mutation based upon phenotype matching

**Human**

**WT**

**mut**

**PAX6**
- cornea opaque
- iris absent
- retina degenerate
- lens opaque
- aqueous humor of eyeball increased pressure

**Pax6**
- eye decreased size
- lens fused to cornea
- iris morphology anterior chamber absent

**pax6b**
- eye decreased size
- lens decreased size
- retina malformed

**ey**
- eye absent

**Mouse**

**Zebrafish**

**Drosophila**

*Linking Human Diseases to Animal Models Using Ontology-Based Phenotype Annotation*
- 13,182 phenotype terms
- 155,624 rare disease - phenotype annotations
- 136,268 common disease - phenotype annotations
Each nosology is different, they inconsistently map to each other, leading to poor interoperability and computability.
If you treat the xrefs as equivalents, then you end up collapsing things and end up with incorrect equivalences (in red)
Defining disease and clinical pathogenicity: A lumping and splitting problem

One disease or two? What does the evidence favor?

- Distinct molecular mechanisms?
  - NO
  - Reputable assertion of difference?
    - YES
    - Distinct clinical management?
      - YES
      - Distinct phenotypic profiles?
        - YES

One disease or two? How do we manage identifiers, hierarchy?

- Split/merge
- Manage resolution & provenance
- Source IDs

MONDO Unified Disease Ontology

Harmonizing diseases, phenotypes, anatomy, and genotypes

91% of our 2.2 Million G2P associations require integrating two or more data sources
Fuzzy Phenotype Matching

Legend
- Perfect Match
- Fuzzy Match
- No Match

Patient P1 profile (3 year old girl):
- None
- Cone-shaped epiphysis of the phalanges of the hand (HP:0003510)
- Delayed speech and language development (HP:0007960)
- Global developmental delay (HP:0001263)
- Microcephaly (HP:0001252)
- Proportionate short stature (HP:0003508)
- Thick upper lip vermilion (HP:000215)
- Hypertelorism (HP:0003934)

Wiedemann Steiner syndrome profile:
- Short toe (HP:0001831)
- Short middle phalanx of finger (HP:000319)
- Delayed speech and language development (HP:0007950)
- Intellectual disability (HP:0001249)
- Microcephaly* (HP:0000252)
- Short stature (HP:00034322)
- Thin upper lip vermilion (HP:0000215)
- Hypertelorism (HP:0003934)

Patient P8 profile (14 year old boy):
- Long toe (HP:0001831)
- None
- Delayed speech and language development (HP:0007950)
- Global developmental delay (HP:0001263)
- Macrocephaly (HP:0003250)
- None
- None
- None
- None
- None
- None
- Biepharophimosis (HP:0000591)
- Biepharophimosis (HP:0003681)
- Epicanthus inversus (HP:0000637)

not same variant, but same disease & gene
KMT2A

DOI: 10.1126/scitranslmed.3009262
Example case solved by Exomiser

Ranked STIM-1 variant maximally pathogenic based on cross-species G2P data, in the absence of traditional data sources

https://exomiser.github.io/Exomiser/

**Phenotypic profile**

**Genes**

- Heterozygous, missense mutation
  - STIM-1

- Heterozygous, missense mutation
  - STIM-1

N/A
Scalable service for Genomics England

- Exomiser is part of the Genomics England pipeline and results presented back to NHS on all cases
- Available-on-demand service returns results in 5 mins/case and linearly scalable: 250 cases/day per processor node
- ISO accreditation verification on 62 random, solved cases

<table>
<thead>
<tr>
<th></th>
<th>Current production</th>
<th>Next release</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exomiser top ranked candidate</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>Exomiser top 3 ranked candidates</td>
<td>89%</td>
<td>94%</td>
</tr>
<tr>
<td>Exomiser top 5 ranked candidates</td>
<td>92%</td>
<td>97%</td>
</tr>
</tbody>
</table>
Retrospective evaluation on solved cases

68% of diagnoses

80% of diagnoses

83% of diagnoses

Missed diagnoses
- 5% non-penetrant
- 1% non-coding
- 1% low quality variant calls
- 2% high minor allele frequency
- 2% low-scoring phenotype matches

Genomics England

Recall/Sensitivity • Precision/Positive Predictive Value (PPV)
Jessica (aged 4) has a rare condition which causes epilepsy, affects her movement and developmental delay. Standard genetics tests negative.

- De novo deletion in SLC2A1 identified as the cause of her Glut 1 deficiency syndrome
- Exomiser ranked this variant first
- Now being successfully treated with a ketogenic, low-carb diet
- Low risk for future pregnancies
Patients and families should be empowered to help...
Example plain-language terms

- Proptosis: Bulging eyes
- Micrognathia: Small jaw
- Impaired Pulmonary Function: Trouble Breathing
- Arachnodactyly: Spider fingers
- Mitral valve prolapse: Heart murmur
Layperson synonyms disease coverage

- **Lay synonyms in numbers**
  - 4,555
  - 7,607

- **Number of HPO terms that have lay synonyms**
- **Number of lay synonyms total**

- **Term coverage**
  - 35%

- **Percent of all HPO terms with at least one layperson synonym.**

- **Disease coverage**
  - 60%

- **Percent of all disease annotations (73,932 of 122,120) that refer to an HPO term that has lay translations**
How many terms can you take away and still recognize the disease?
How much phenotyping is enough?

- Hair present on head (7)
- Dark hair (6)
- Male (4)
- Female (4)
- Enlarged lip (2)
- Enlarged ears (2)
- Increased skin pigmentation (3)
- Hair absent on head (1)
- Horns present (1)
- Pointy ears (1)
- Blue skin (1)

bit.ly/annotationsufficiency
How diagnostically useful are the HPO terms generated by patients?

Actual mileage (for a given disease) may vary depending on its layperson-coverage of the corresponding phenotypes.
An example comparison of simulated profiles relative to gold standard

Legend

- Perfect Match
- Fuzzy Match
- No Match
For 7667 MONDO diseases: What is the diagnostic power of HPO LaySlim vs GC Subsets as compared to Gold Standard Annotations?

Number of terms for 7667 MONDO diseases:

- What is the diagnostic power of HPO LaySlim vs GC Subsets as compared to Gold Standard Annotations?

Number of diseases ranked within the top 5 of most phenotypically similar to the correct diagnosis when gold-standard clinical HPO annotation profile is constrained by the terms available in LaySlim or by terms mapped to GC. These simulated profiles can be assessed according to their diagnostic power.

When any profile is further constrained by deleted terms or less specific terms general, the diagnostic power reduces as expected.

Algorithm: Boqa

Algorithm: Phenodigm
Layperson-HPO driven phenotyping tool: body.phenotypyr.org

Standard exchange formats exist for genes … but for phenotypes? Environment?

http://phenopackets.org
Finding the sweet spot between simple and expressive

Ease of use

Expressivity

List
CSV
CDEs

The gap

Global Alliance for Genomics & Health
Craniosynostosis

HP:0001363
List of terms...

Craniosynostosis
Brachydactyly
Proptosis
Broad thumb
Can we do better?

- Craniosynostosis
- Brachydactyly
- Proptosis
- Broad thumb...

How are these linked to a patient? What about the parents and siblings?

Were they NOT observed?

When were they first observed?

How severe are these?

Are some more severe than others?
We need structure!

**Patient:**
- **ID:** "PROBAND#1"
- **Sex:** "male"

**Phenotypes:**
- **Type:**
  - **ID:** "HP:0000520"
  - **Label:** "Proptosis"
- **Severity:**
  - **ID:** "HP:0012828"
  - **Label:** "Severe"
- **Class of Onset:**
  - **ID:** "HP:0003577"
  - **Label:** "Congenital onset"
Phenopacket Implementations

• Reference implementation/spec:
  • Phenopacket-schema GitHub repo (https://github.com/phenopackets/phenopacket-schema)
• Proof of concept applications:
  • Exomiser web (Monarch web-app) (bit.ly/phenopacket-app-beta)
  • FHIR -> Phenopacket service
  • Exomiser service
  • SMART on FHIR app
• In production systems:
  • Biosamples exporting Phenopackets (e.g. https://www.ebi.ac.uk/biosamples/samples/SAMN05324082)
Conclusions

Ontologies can be used to harmonize phenotypes across patients, diseases, and species, aiding disease diagnosis.

Use of integrated phenotype & other basic research data has improved diagnostic rate in GEL to >95% in top 5.

Patients are a key source of phenotypic information and both patients and clinicians need to participate to maximize diagnostic capabilities.

Next steps: Validate EHR phenopackets extraction for genomic pipelines. Support labs/registry/journal submission. Pedigree/family history.
Deeper phenotyping is a collaboration

- Patient self-description
- Basic research
- Clinicians
The Monarch Initiative

Kent Shefchek
Nicole Vasilevsky
Matt Brush
Julie McMurry
Catherine Brownstein
Ingrid Holm
Jules Jacobsen
Peter Robinson
Sebastian Koeller
Chris Mungall
Jim Balhoff
Tudor Groza
David
Osumi-Sutherland

www.monarchinitiative.org

Funding:
PCORI: ME-1511-33184
NIH Office of Director:
2R24OD011883