mendelian

Search Performance on real cases

Only half the patients referred to a clinical geneticist for diagnosis of a genetic disorder will be diagnosed. Those patients may subsequently be referred to several physicians, undergo numerous clinical tests and if lucky be offered next-generation genome sequencing to search for causative genes.

Of those referred for genome sequencing, only about 25% will eventually get a confirmed diagnosis. On average, it takes 5.6 years in the UK for a rare disease patient to be diagnosed[1].

Background

Mendelian is an online rare disease search engine, built with the aim of increasing diagnostic hit rates. Rare diseases, their associated genes along with existing gene panels, are algorithmically matched to phenotypes.

The aim of this report, addressed to health professionals and clinicians, is to provide the simple metrics for the likelihood of finding a successful diagnosis through Mendelian.

How is Mendelian used?

Confronted with a rare disease case, a medical professional would enter their patient's clinical features into app.mendelian.co. The tool outputs a focused shortlist of genes and diseases for consideration. For each result, Mendelian displays the underlying genetics and potential gene panels.

Related work

There are many tools on the market for analysing genetic sequences for causative variants. Tools like Sophia DDM and Ingenuity have found commercial success in the clinic and research.

As variant analysis has advanced, there has been exciting work in integrating phenotypic information to improve variant prioritisation. Examples include Exomizer[2], PheVor[3] and Phenolyzer[4].

This study[5] (Melbourne Genomic Health Alliance - MGHA) has since shown that semi-automatic solutions can outperform fully-automated solutions in the clinic. In this approach clinicians curate candidate genes before the computational analysis takes place. In this study, we will compare tools that can perform this curation against a team of expert clinicians. As of today, the main solutions in the field are Mendelian, Phenomizer[6], FindZebra[7] and Phenotips[8].

Evaluation

We ran Mendelian over the 49 WES diagnoses from the MGHA study. These diagnoses were made by a panel of clinicians given the variant analysis report. They have kindly provided us with the clinical features of their patients (encoded in HPO) and the responses of Phenomizer, Phenotips and their panel of clinicians (before variant analysis). Each response was a gene list for evaluation against the

true causative gene.

Panel of clinicians: this is a candidate gene list created by a referring clinician, seven geneticists, two metabolic physicians and two pediatric neurologists. These lists ranged from 1-161 genes long with a median of 23.

Phenomizer: we consider the top hundred differential diagnoses for the patient's HPO terms.

Phenotips: we consider the suggested diagnoses section created by phenotips

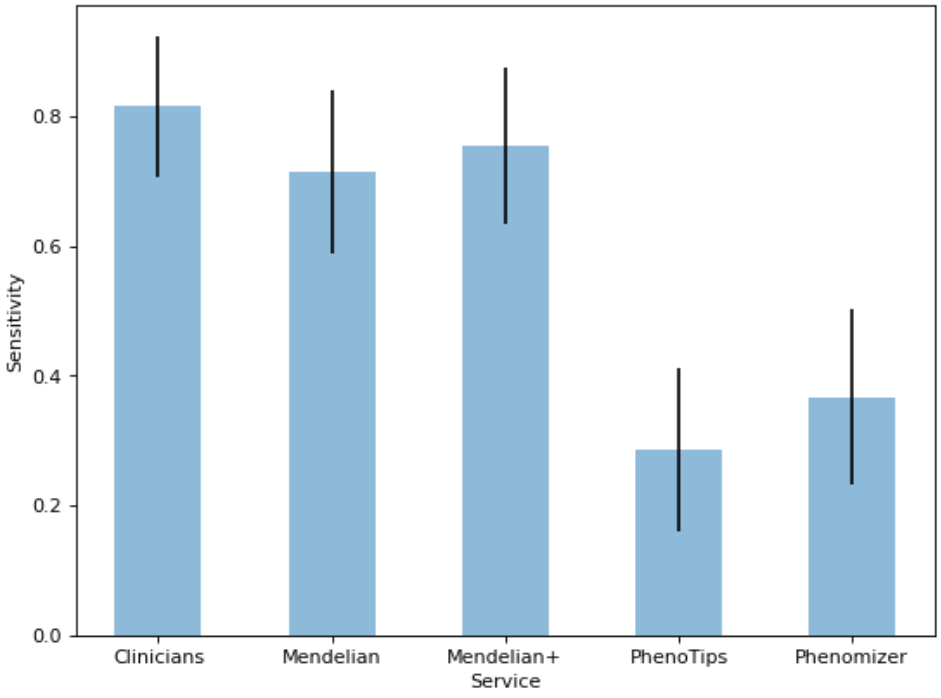
Mendelian: as with Phenomizer we consider the top hundred diagnoses. A diagnosis is considered correct if it links to the OMIM disease or gene provided by MGHA.

Mendelian+: as with Mendelian, except we simulate a clinician's response to the top suggested HPO term from our suggestion engine.

Comparison of Sensitivity

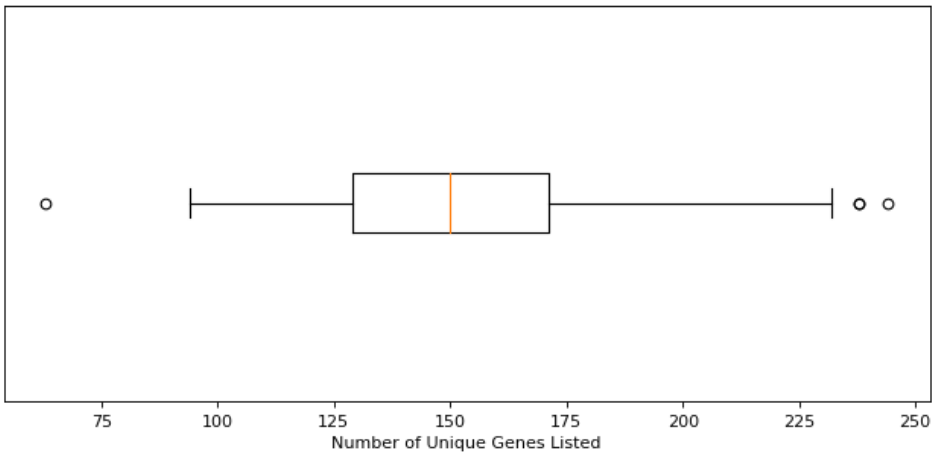
We can make a rough comparison of sensitivity by computing the number of correct predictions / number of predictions. There are a few caveats to this comparison:

- The automated tools predict diseases or disease groups, which could have none or many known genetic bases. (Mendelian tries to find the most specific diagnosis possible)
- The panel of clinicians provide a gene list of up to 161 genes whereas Phenotips suggests around 20 matching diagnoses for each patient.
- Error bars are calculated at the 90% confidence interval



Comparison of Genes List Size

For Mendelian we can get an idea for the number of genes returned in the top 100 results:



Discussion

Mendelian's sensitivity is approaching that of expert clinicians. There is a marked improvement compared to the automated solutions evaluated by MGHA.

One explanation for this is the comprehensiveness of the different knowledge bases. Mendelian aggregates various databases as well as extracting knowledge from PubMed. Whereas Phenomizer is limited to OMIM, Orphanet and DECIPHER; and Phenotips to OMIM.

Another consideration is the difference in knowledge-bases between the studies. The MGHA study was conducted a year prior to this one. It is possible that there were several discoveries in rare disease research that have since made certain cases easier to diagnose.

The gene list size is the main differentiating factor between Mendelian and the expert clinicians. The clinicians still provide the best curation, achieving the highest sensitivity for the smallest gene lists. But we suspect that a broader gene list could increase the sensitivity of a diagnosis system. These knock-on effects would have to be investigated in a follow-up paper.

Clinicians performed better on cases with less distinct clinical histories. For example, Mendelian occasionally missed cases that contained common terms like *Seizures*, *Hypotonia* and *Global Developmental Delay*. Each of these terms are associated to thousands of rare diseases making it more difficult to differentiate between them.

Mendelian was able to identify 4 genes missed by clinicians DYNC2H1, ECHS1D, STAT1, NALCN. Most of these cases were described with very distinct features like "*Chin with horizontal crease*" and "*Desquamation of skin soon after birth*". All of these cases were too rare to have prevalence information on Orphanet.

Conclusion

Mendelian is the only automatic solution that is able to curate specific gene lists with a sensitivity close to that of a panel of expert clinicians. It has complementary strengths to the clinicians, performing better on very rare cases. This makes it a good candidate for semi-automatic curation.

Expert clinicians are experienced enough to correctly predict genes even for poorly described patients. Future work could explore emulating this in the automated systems by integrating epidemiological data, in the absence of phenotypic data.

The panel of clinicians were unable to diagnose 33 patients in the MGHA study, which we did not have access to. It would be interesting to see if a Mendelian-assisted curation of genes reveals viable diagnoses for these cases.

References

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