Automated HPO terms matching reduces analysis time but does not completely eliminate the requirement for manual review of exome sequencing results

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A crucial step of diagnostic exome sequencing (DES) is determining which alterations have clinical relevance to the patient. DES of a proband alone yields 30-100 unique rare variant-containing genes with at least one established Mendelian gene-disease relationship. Assessment of clinical relevance to the proband's phenotype can be done either manually or computationally by matching the proband's HPO terms with HPO terms associated with genes (https://hpo.jax.org/app/). The latter method can be faster and is becoming common in clinical testing, but it is unclear whether it is as comprehensive as manual review, especially for newly established gene-disease relationships.

We compared manual and computational methods of assessing clinical relevance of genes in 35 proband-only cases whose exomes were sequenced at our clinical laboratory. Assessment of clinical relevance was first carried out manually by PhD-level scientists and then by an internally developed machine learning-based algorithm which ranked genes based on their scores reflecting the magnitude of clinical relevance. Genes with scores below an empirically derived cutoff were considered unreportable without additional review. The remaining genes were reviewed to confirm the appropriateness of the computationally derived clinical relevance.

Manual assessment found 21 patients with at least one reportable alteration in a clinically relevant gene amounting to 28 unique genes in total. Our computational method ranked 24/28 (85.7%) of these genes above the cutoff for clinical relevance, of which 18 (75%) were ranked in the top five clinically relevant genes. Three genes were below the cutoff and one gene (*SETD1A*) could not be ranked due to the lack of associated HPO terms in the HPO database despite being a known Mendelian disease gene. The reasons that the 3 genes were ranked below the cutoff by the algorithm were (1) a highly variable disease spectrum of the gene prevented the algorithm from assigning it a high score (*MANBA*), (2) a new -gene-disease association in the literature was not yet reflected in the HPO database (*HK1*), and (3) ambiguous nature of the input HPO terms describing the patient's clinical phenotype (*GHSR*). On average, 51 genes were manually assessed for each patient, whereas after HPO ranking the number was 21. 57.1% of genes per patient were ranked under the cutoff by the algorithm (i.e. clinically irrelevant) which amounted to a 24.1% reduction in time spent confirming clinical assessment relative to the manual review alone.

Computational assessment of clinical relevance saves time, but manual review of low-ranking genes is also needed to avoid false negatives. Updating the gene-HPO terms database as soon as new gene-disease associations are published will minimize these false negatives.