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Bridging the language gap - A call for the wider use of Human phenotype ontology by non-geneticist clinicians when requesting genomic tests

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ABSTRACT

Advances in genomic technology including the development of next-generation sequencing (NGS) have enabled the identification of thousands of variations at a time, allowing the discovery of novel genetic diseases. Given the volume of data generated by these investigations, attention is drawn towards reporting relevant clinical features by clinicians to guide the diagnosis and management of their patients. The Human Phenotype Ontology (HPO) developed in 2008, revolutionized the semantic vocabulary of phenotypic descriptions in genomic medicine allowing researchers, laboratories and clinical geneticists to better understand each other. In this era of personalized medicine where genetic tests are becoming more accessible, non-geneticist clinicians are expected to be more involved than ever in the process of ordering genetic tests and interpreting genetic reports. It is therefore essential that they understand and adequately apply HPO nomenclature to integrate the patient care chain and seize the opportunity offered by this tailored language. The current article highlights the importance of using HPO vocabularies in clinical practice and advocates for its wider use by non-geneticist clinicians. Correct use of HPO will reduce misunderstandings between healthcare professionals and ultimately improve the healthcare system.

1. Introduction

Access to cutting-edge genomic sequencing technologies has facilitated the diagnosis and management of genetic diseases in routine clinical practice. In the age of precision medicine, clinicians without specialist training in genetics (e.g., neurologists, cardiologists, paediatricians, oncologists, ophthalmologists etc.) are increasingly being encouraged to request genetic tests directly from the clinic based on their interpretation of patients' clinical phenotype (Salm et al., 2014). However, modern clinical genetic testing typically comprises either multi-gene panels, exome or genome sequencing whose interpretation rely heavily on phenotypic details conveyed to the laboratory. Such descriptions are often subjective, inaccurate, or incomplete (Nickel et al., 2017). Inappropriate exchange of information between clinicians and laboratories may result in diagnostic errors through failure to request the correct test or through errors in variant interpretation where phenotypic terms have been incomplete, incorrect, or misinterpreted.

Important steps are being taken by various clinical laboratories to efficiently and accurately extract Human Phenotype Ontology (HPO) terms from test requisition forms using combinations of bioinformatics and machine learning-based methods. Nevertheless, having incomplete or inappropriate phenotypic features remains a limiting factor to the provision of accurate diagnosis (Deisseroth et al., 2019). Using examples related to a single rare condition, the achalasia-Addison's-alacrima syndrome also known as Allgrove or triple A syndrome (Online Mendelian Inheritance on Man-OMIM: 231550), we will highlight the importance of accurate and precise phenotyping in genetic test requests. Then, we will discuss the utility and practical applications of the Human Phenotype Ontology (HPO) for non-geneticist clinicians.

1.1. Importance of using an accurate and precise phenotype vocabulary

Pre-analytical errors in laboratory testing include incomplete requisition forms and inadequate test orders. In most healthcare

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systems, especially in the National Health Service in England, when ordering genetic tests for patients, clinicians provide a lab requisition form containing a full and complete description of the clinical features as requested by the ISO 15189 International Standard (clause 5.4.3) (Accuracy, 1994). An accurate description facilitates mutual understanding between clinicians and laboratory specialists and allow an easy selection of the appropriate genomic test by the physician based on potential and differential diagnosis. However, the vocabulary used to convey this information may differ from one clinician to the other and from one discipline to the next, thus often creating confusion.

For example, the expressions "adrenal hypoplasia" and "corticotropin insufficiency" would not have the same meaning for a laboratory geneticist and may relate to different diseases and genes during the interpretation even though patients may have similar phenotypes. Providing additional details of the patient's clinical presentation would increase the likelihood of finding the right variant and identify additional and incidental findings (other variant not related to phenotype may be identified) and reduce investigation time. The information provided by the clinicians guide the laboratory throughout analysis, interpretation and reporting of the significant findings. Furthermore, the clinical description needs to be precise; a description as "patient crying without tears" could refer to alacrima (reduced or absent tear production) in the Allgrove syndrome, but it could also describe over 13 different genetic disorders, plus some multisystem rheumatic disorders such as Sjogren syndrome (Adams and Schaaf, 2018).

Furthermore, to improve the diagnosis of rare diseases and cancer by clinicians, there are emerging technologies such as the Schema Phenopacket (Jacobsen et al., 2022). Developed by the Global Alliance for Genomics and Health (GA4GH) (https://github.com/phenopackets/), it allows the clinician to up-date disease status in the catalogs and provide phenotypic or non-phenotypic medical data. Thus, it facilitates deep phenotypic investigations per patient and extends the use of HPO as a common language between the different users.

1.2. Importance and implications of HPO in genetic testing

Given the huge variations in terminology across practices and specialties, the use of a standardized nomenclature is crucial to improve the precision of phenotypic descriptions on test requisition forms. Initially designed for rare diseases, the Human Phenotype Ontology (HPO) has become a widely adopted and standardized terminology of phenotypic abnormalities associated with over 8000 diseases (Groza et al., 2015; Robinson et al., 2008; Köhler et al., 2021). HPO provides accurate, precise, and standardized terminology to facilitate communication and data sharing between clinicians and genetic experts. It can allow rapid detection of phenotypic similarities between diseases and connect them to the OMIM database, thus enabling direct traceback of diseases (Robinson et al., 2008). HPO brings a consensus language between geneticists, non-geneticist clinicians, laboratories and biomedical researchers, thus making published studies or record comparable and data sharing more convenient.

For clinicians, using the HPO nomenclature also gives the possibility to explore two main diagnostic approaches: a phenotype-based approach and a genotype-driven approach.

1.2.1. Phenotype-based approach

Requesting genetic tests for a patient involves a precise description of the clinical phenotype just as it is done when ordering other clinical investigations (e.g., an MRI scan). With HPO, clinicians can conveniently input relevant phenotypes in the repository, retrieve a list of candidate diseases or genes and use it to decide which genetic test to request. Providing exact and specific clinical descriptions will improve the choice of the precise test needed and the cost-effectiveness of the genetic explorations. By using HPO terms, with software like Phenomizer (https://compbio.charite.de/phenomizer/), it is possible to enter clinical information and select candidate genes to test. For instance, in a patient presenting with triple A syndrome, entering only achalasia (HP:0002571) and alacrima (HP:0000522) in the Phenomizer gives a set of 5 candidate genes. However, when adding Addison disease (HP:0008207), it reduces to 3 candidate genes including the *AAAS* gene (giving a significant p-value of similarity with the HPO combination of terms $p < 0.05$) thus pointing towards a gene panel or a more targeted testing. Consequently, with HPO terms, the clinician can go back to the bedside and look for extra-findings that could be submitted to the web tool to narrow the differential diagnosis. This approach is less expensive and selective. If the selected test is negative, the clinician can then consider a broader test with more genome coverage. This process provides an excellent overview of the patient's disease and enables physicians to explore potential diagnoses and consider referring their patients to the appropriate specialist even before receiving test results. It is arguably the best approach when the phenotype is well known and highly specific, but it is less convenient in the context of atypical clinical presentations. Besides, it empowers clinicians and reduces the time required to reach a final diagnosis and initiate the appropriate treatment if any.

Moreover, providing details on ethnicity, gender and age also helps to narrow the scope of the tests performed. Indeed, some disorders are common in certain population groups. If a patient with features of Allgrove's syndrome (OMIM: 231550) also exhibits dysautonomia, for example, knowing that the patient is of Ashkenazi Jewish descent would encourage the laboratory to advise a screening for the *ELP1* gene (OMIM: 603722) that can cause similar clinical features (Shvartsbeyn et al., 2011).

1.2.2. The genotype-based approach

Given that genetic heterogeneity is a primary concern when investigating genetic diseases, some clinicians can opt for a genotype-driven approach, allowing a full exploration of genetic etiologies with a broad test, especially if the phenotype is not clear or specific. This is the main approach in clinical practice. Together with the precision and specificity of HPO, this approach is powerful for both diagnostic and research purposes. Basically, to interpret the results of exome or genome sequencing, information on clinical phenotype is essential. An initial search involves ascertaining if the region containing the variant can cause a similar phenotype. After performing the analyses, the laboratory can browse online databases associating genetic diseases with their related phenotypes to check if the clinical description matches the phenotypic description provided by the clinician. Examples of such online databases include OMIM (see https://www.omim.org) and UniProtKB (see https://www.uniprot.org/help/uniprotkb). Again, to find true causal variants among hundreds of thousands of variants, some filters can be applied to perform candidate variant selection based on the phenotype in software like Exomizer, Phenomizer, and PhenIX (Pengelly et al., 2017).

Additionally, to interrogate variant pathogenicity, it is necessary to look through published literature and databases to find evidence of previously described similar clinical features in other patients or families (allelic data, segregation data, other databases, and other data criteria). (Richards et al., 2015).

2. Conclusion and perspectives

Requests for genomic testing are on the rise and non-geneticist specialists are increasingly involved. However, some important challenges faced by non-geneticist clinicians in clinical settings include selection of the adequate test and analyzing reports. In routine clinical practice, the use of patients' phenotype to guide clinical genetic testing is limited by atypical clinical presentations. Atypical clinical presentations are well-known by clinicians as features that do not read the books. Although not a perfect system, HPO terms not widely used by non-geneticist clinicians is a strong alternative which can improve the accuracy and precision of their phenotypic description. This provides several benefits

for both professionals and patients, including reduction of the pre-analytic errors of genetic tests, better communication between professionals, and shortening of the diagnostic odyssey. Nevertheless, as laboratory testing results should always be contextualized, including interpretation of variants of uncertain significance, non-geneticist clinicians should consider seeking advice from genetic counselors, and clinical geneticists in a multidisciplinary approach whenever possible. A standardized vocabulary among all stakeholders may be a powerful tool in decision-making. Considering these benefits, it may be useful to introduce specific training modules on the use of HPO nomenclature both in medical school curricula and in post-graduate clinical training programs.

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CRediT authorship contribution statement

Larissa Ange Tchuisseu-Kwangoua: Conceptualization, and design, Writing – original draft. **Joseph Kamtchum-Tatuene:** Writing – review & editing, All authors approved the final version. **Cedrik Tekendo-Ngongang:** Writing – review & editing, All authors approved the final version. **Reuben J. Pengelly:** Writing – review & editing, All authors approved the final version. **Jay Self:** Writing – review & editing, All authors approved the final version.

Data availability

No data was used for the research described in the article.

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References

Accuracy, I.S.O., 1994. (trueness and Precision) of Measurement Methods and Results — Part 1: General Principles and Definitions. ISO (the International Organization for Standardization).

Adams, J., Schaaf, C.P., 2018. Diagnosis and genetics of alacrima. Clin. Genet. 94 (1), 54–60.

Deisseroth, C.A., Birgmeier, J., Bodle, E.E., Kohler, J.N., Matalon, D.R., Nazarenko, Y., et al., 2019. ClinPhen extracts and prioritizes patient phenotypes directly from medical records to expedite genetic disease diagnosis. Genet. Med. 21 (7), 1585–1593.

Groza, T., Kohler, S., Moldenhauer, D., Vasilevsky, N., Baynam, G., Zemojtel, T., et al., 2015. The human phenotype Ontology: semantic unification of common and rare disease. Am. J. Hum. Genet. 97 (1), 111–124.

Jacobsen, J.O.B., Baudis, M., Baynam, G.S., Beckmann, J.S., Beltran, S., Buske, O.J., et al., 2022. The GA4GH Phenopacket schema defines a computable representation of clinical data. Nat. Biotechnol. 40 (6), 817–820.

Köhler, S., Gargano, M., Matentzoglu, N., Carmody, L.C., Lewis-Smith, D., Vasilevsky, N. A., et al., 2021. The human phenotype Ontology in 2021. Nucleic Acids Res. 49 (D1). D1207-d17.

Nickel, B., Barratt, A., Copp, T., Moynihan, R., McCaffery, K., 2017. Words do matter: a systematic review on how different terminology for the same condition influences management preferences. BMJ Open 7 (7), e014129.

Pengelly, R.J., Alom, T., Zhang, Z., Hunt, D., Ennis, S., Collins, A., 2017. Evaluating phenotype-driven approaches for genetic diagnoses from exomes in a clinical setting. Sci. Rep. 7 (1), 13509.

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., et al., 2015. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. Genet. Med. 17 (5), 405–424.

Robinson, P.N., Kohler, S., Bauer, S., Seelow, D., Horn, D., Mundlos, S., 2008. The Human Phenotype Ontology: a tool for annotating and analyzing human hereditary disease. Am. J. Hum. Genet. 83 (5), 610–615.

Salm, M., Abbate, K., Appelbaum, P., Ottman, R., Chung, W., Marder, K., et al., 2014. Use of genetic tests among neurologists and psychiatrists: knowledge, attitudes, behaviors, and needs for training. J. Genet. Counsel. 23 (2), 156–163.

Shvartsbeyn, M., Rapkiewicz, A., Axelrod, F., Kaufmann, H., 2011. Increased incidence of tumors with the ikbkap gene mutation? A case report and review of the literature. World J. Oncol. 2 (1), 41–44.