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Studying from Data can be used to Recognise Severe Infants with Genetic Illnesses

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Abstract

Mendelian disorders are prevalent in neonatal and pediatric intensive care units and are a major cause of morbidity and mortality in these facilities. Current diagnostic pipelines that integrate phenotypic and genotypic data are expert-dependent and time-consuming. Artificial intelligence (AI) tools can help solve these challenges. Analyze the patient's phenotype and genotype to establish an orderly differential diagnosis. We used Dx29 to retrospectively analyze 25 acutely ill infants diagnosed with Mendelian disorders using a targeted panel of approximately 5000 genes. For each case, trio files (subject and parents) were analyzed using information on genetic mutations and patient phenotypes provided to Dx29 through three approaches. AI extraction with manual review/editing, and manual entry. Next, we determined the rank of the positive diagnosis in the differential diagnosis of Dx29. Using these three approaches; Dx29 placed the correct diagnosis in the top 10 with 92-96% probability. These results are due to the use of automated phenotyping of her Dx29 by a layman followed by data analysis compared to the standard workflow developed by Bioinformatics by the expert used for the analysis. Suggests that Genomic data and diagnosis of Mendelian disease may be informative.

Keywords: Natural language processing; Genomics; Computer assisted diagnosis; Pediatrics; Neonatal; Intensive care unit

Introduction

Mendelian disorders, hereditary disorders with a single gene, are prevalent in neonatal and pediatric intensive care units (NICU/PICU) and are associated with significant morbidity and mortality. Rapid diagnosis of Mendelian disorders may influence clinical decision-making and lead to better outcomes [1]. However, these diseases often have multiple causes and different symptoms, making diagnosis difficult. Advances in genome-wide sequencing, such as exome and genome sequencing (ES and GS), have enabled clinicians to address this challenge in patients with suspected Mendelian disorders. However, several barriers to mainstream adoption of these technologies remain, including training of frontline medical professionals, high costs, and complex data analysis processes. ES and GS occur in two general steps: First, extraction and sequencing of DNA from patient samples (blood, saliva, etc.). Second: analysis of sequence data. Mutants are identified by comparing the sequences to genomic standards. The variants are then filtered according to the analyst's parameters (such as population frequency) to identify the variants most likely to cause disease [2]. In addition to genomic analysis, manual review of patient medical records identifies important phenotypic traits that guide the diagnostic process. Standard diagnostic pipelines that integrate patient phenotypic and genotypic information are time consuming. Even if the pipeline is optimized quickly, diagnosis can take days or weeks. These processes also rely on extensive genetics and bioinformatics expertise. For NICUs and ICUs not affiliated with university medical centers, access to this expertise may be limited. There are over 23,000 intensive care beds in approximately 1,400 hospitals in the United States [3]. He is estimated to have less than a third of these hospitals affiliated with academic institutions. Integrating artificial intelligence (AI) into these analytics pipelines is an active research area that can help fill this knowledge gap.

AI has been applied to clinical genomics in a number of ways. A prominent example is the use of natural language processing (NLP), an AI technology that enables the analysis of unstructured text, to automatically generate phenotypic information about patients through the analysis of medical records, thereby improving genetics [4]. To assist in diagnosing patients with sexually transmitted diseases. Extracted; automated phenotyping combined with patient genetic data can reduce the time from DNA sequencing to diagnosis.

Greater access to the genetic diagnostic process in neonatal wards and intensive care units has the potential to bring many benefits, including reduced costs and increased use of new technologies such as ES and GS. It may also facilitate patient reanalysis as the patient's clinical condition progresses [5]. Verification of accessible open-source tools like Dx29 is therefore essential. This study tested her ability of Dx29 to retrospectively identify the correct Mendelian disease in infants with previously diagnosed acute illness in the NICU and ICU. These infants were diagnosed through a typical genomic diagnostic pipeline using a targeted sequencing panel called RapSeq (ARUP Laboratories, Salt Lake City, UT, USA) [6].

Materials and Methods

Participants

We retrospectively analyzed 25 trios (infants + parents) that met the following two criteria: The child was admitted to the NICU or ICU. The infant was diagnosed with Mendelian disorder using her RapSeq, a targeted panel of ~5,000 genes covering most known disease-causing genes [7].

Dx29: Technology and data protection

Dx29 uses NLP powered by Microsoft Text Analytics for Health (Microsoft Corporation, Redmond, WA, USA) to identify symptoms and signs in medical records and converts this data into a standardized

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hierarchy of phenotypic descriptors. Convert to Human Phenotype Ontology (HPO) terms. To create a differential diagnosis based on phenotypic and genotypic information, Dx29 uses the open source tool Atomizer [8]. To base differential diagnosis solely on phenotypic information, Dx29 compares the patient's phenotype with information in her Orphaned and OMIM databases to identify likely disease candidates.

Dx29 is hosted on Microsoft Azure servers with identity management services, threat protection, compliance tools, data protection tools, and encryption mechanisms for data at rest and in transit to ensure the privacy and security of patient medical information. Patient data can also be pulled from her Dx29 at any time by the patient [9].

Results

In a previous report, patients were enrolled in the RapSeq study to assess the diagnostic capabilities of a genome-wide rapid panel of approximately 5,000 genes in the NICU. RapSeq's diagnostic pipeline is skills-based and requires manual review of patient records to identify phenotypic traits salient as HPO terms. HPO terms are associated with variant analysis pipelines to arrive at a final diagnosis. Twenty-five trios previously sequenced and analyzed in the RapSeq study were selected for analysis by Dx29 [10]. The genes involved and her OMIM diagnosis in each case should be noted. At the time of this study, Dx29 was not set to predict negative results. A differential diagnosis was performed in each case regardless of whether a possible candidate disease was identified. Moreover, the Dx29 cleavage site did not allow us to study each mutant and potential disease sufficiently to rule out a diagnosis with this cleavage site alone. Therefore, only RapSeq-positive cases that led to the identification of variants that explained the patient's phenotype were included.

Discussion

Standard diagnostic pipelines for analyzing genome-wide sequence data and diagnosing rare inherited diseases remain complex and often rely on extensive genetic and bioinformatics expertise. Dx29 is an AI-based clinical tool designed to streamline this process by rapidly identifying a list of genetic disorders that may be associated with a patient's clinical symptoms. Our data suggest that fully automated use of Dx29 or a similar tool in the presence of a positive genetic diagnosis can efficiently and accurately identify a candidate list of potential diagnoses for 10 diseases. Further development of these systems may represent a new paradigm for supporting NICU and ICU physicians caring for patients who may be affected by genetic diseases.

Manual reanalysis of his HPO terms after automatic extraction by Dx29 increased the time required to generate a ranked differential diagnosis. However, it took less than 3 hours on average. Our data suggest that manual reanalysis may improve the accuracy of his Dx29, but the improvement was limited. There was no difference in identifying the correct diagnosis for the top 5 symptoms, 88% in both cases. There was also a modest improvement in the top 10 symptoms from 92% to 96% of cases, although this may require improvement. Future studies with larger cohorts will confirm. Therefore, the data presented here support the automatic use of Dx29 and corroborate the effectiveness of the algorithm used.

We report here that manual review of automatically extracted phenotypes resulted in the removal of an average of 59% of HPO terms extracted by Dx29. In the final list of candidate disorders, the ranking of the accurate diagnosis only saw a slight improvement, as was already mentioned. Others incorrect terms were identified out of context; for instance, comments made about a patient's chin during the physical exam led to Dx29 extracting the HPO term "abnormality of the chin." While many of the terms that we removed were errors made by the NLP algorithms used by Dx29 (e.g., "cerebral palsy" being identified in a document that uses the abbreviation for some other purpose), others were identified incorrectly. Dx29's ability to perform nearly as well when these false phrases were taken into account as when they were eliminated demonstrates how its algorithms prioritize on the phenotypic traits crucial for a particular genetic disease's diagnosis. The fact that numerous terms appropriately extracted from patient data were not always connected to the patient's final diagnosis serves as more evidence of this. For instance, even when the patient's respiratory distress may be more pertinent to the patient's preterm birth than to his or her genetic disease, Dx29 will accurately assign the related HPO term to the patient. However, when the HPO terms that were discovered through manual examination of patient data and later used in the common diagnostic pipeline were given to Dx29 in place of the automatically extracted terms, we observed no improvement in our results.

The older patients and patients undergoing sequencing in outpatient or inpatient settings outside of the intensive care unit were omitted from this study, which was focused on newborns in intensive care units (NICU and PICU). Future research is required to ascertain how Dx29 or other techniques enhance genetic diagnosis in these patients. Similar to this, Dx29 enables patients or family members to directly enter symptoms into the diagnostic pipeline. To determine how this intriguing capability affects patient and provider engagement, contentment, and faith in the results of genetic diagnostics, more prospective research is required. Despite these drawbacks, our research shed more light on the possible use of AI in the diagnosis of infants with complicated genetic diseases. Dx29 has demonstrated encouraging results when used by non-bioinformatics specialists, and an AI platform comparable to Dx29 may one day enable doctors' genomic analysis and diagnosis without the need for bioinformatics experience. It demonstrates how the procedure could be streamlined.

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