Automated variant classification: maintain quality, support standardised interpretation and reduce turn-around times

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BACKGROUND

As demand for genomic testing increases, driven by greater accessibility and falling sequencing costs, variant analysts are encountering increasingly complex patients in addition to their routine cases. While increased access to testing is to be celebrated, 71% of clinical laboratories report to be at, or near, capacity[1]. Automated processes are commonplace in the diagnostic laboratory; from liquid-handling robotics to automated bioinformatics pipelines processing large volumes of data, however due to the complex nature of interpretation there has been resistance to increase the use of automation in this part of the diagnostic process, despite up to 70% of causal variants recurring in multiple patients [2,3,4].

METHODS

To investigate the potential impact of automating interpretation an audit of 19,116 previously-analysed cases was performed to determine the proportion of recurrent diagnoses. A manual second check of the classifications was performed in three patients to estimate time taken to complete an automated case analysis, compared to cases requiring a full review and report (~90 minutes). In addition to this, an additional six cases were reviewed in which the causal variant was not previously described where 17 of the ACMG criteria were automatically selected and evidenced.

RESULTS

Of **19,116 probands in our cohort, 7530 had at least one pathogenic or likely pathogenic variant (39%)**. 3994 individuals had a pathogenic or likely pathogenic variant previously identified and classified similarly in at least one other individual (21% of all cases, 53% of diagnosed cases), figure 1. Sign-out of these automated results took as little as **5 - 8 minutes per case**, rather than the 90 minutes using our current standard workflow.

Each variant was classified consistently, accompanied by supporting evidence:

- Variant Classification
- Publications
- ACMG criteria, plus supporting evidence
- Comments from previous analyses

Inheritance patterns were also taken into account in the automation process to prevent default reporting of carrier status in unconsented genes. For variants not previously reported, automated selection of 17 of the ACMG criteria saved approximately 30% of the interpretation time of each variant.

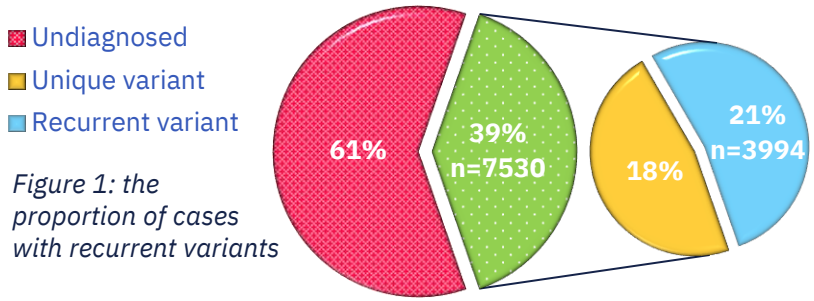


Figure 1: the proportion of cases with recurrent variants

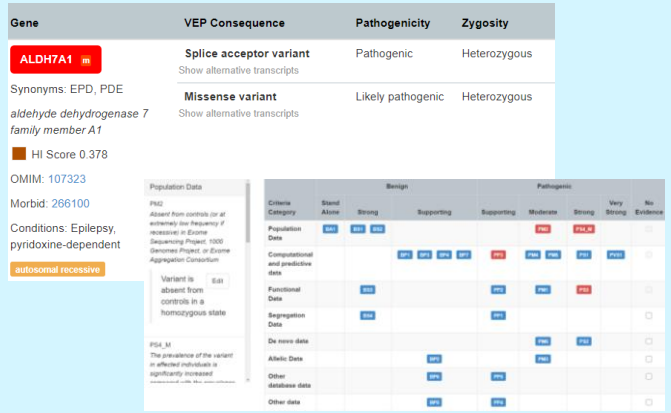
CONCLUSION

Automated classification and evidencing of previously reported variants could **save up to 85 minutes per case**, **standardize interpretation** between users and **reduce turnaround**, particularly in time-critical cases. Results are can be manually second-checked prior to sign-out to ensure clinical-grade results, without the additional need to repeatedly retrieve supporting data and manually assign ACMG criteria. Even partial automation of ACMG criteria selection for novel variants is valuable, further reducing the time to report by 30%. **Streamlining analysis workflows using automated interpretation allows increased throughput, supports better use of resources, while maintaining strict standards in quality and clinical safety.**

CASE STUDY

This patient was referred as a singleton at 11 months old with **neonatal conjugate hyperbilirubinemia, hypotonia**, and was admitted to pediatric intensive care with ***status epilepticus***. Rapid **whole exome sequencing** was performed and the data processed through our automated pipeline, with a **153-gene neonatal epileptic encephalopathy virtual gene panel**.

1. Two variants in the ***ALDH7A1* gene**, associated with autosomal recessive pyridoxine-dependent epilepsy
2. Both variants a**utomatically classified**
3. Second-check and **reporting of these variants took only 8 minutes**
4. Patient **switched from standard anticonvulsant therapy to high-dose pyridoxine,** prior to the onset of any lasting brain damage or encephalopathy



References: 1. PMID: 30686822, 2. PMID: 30847666, 3. PMID: 30847666, 4. PMID: 29100083

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