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 we completed an audit of 19,116 previously-analysed cases from a wide range of referrals to determine the proportion of diagnoses that could have been made if previously-interpreted variants did not require full re-interpretation each time they were observed. We performed a manual second-check of the variant classifications in three patients to estimate time taken to complete an automated case analysis, compared to cases requiring a full review and report (~90 minutes).

RESULTS

Of **19,116 probands in our cohort, 7530 had at least one variant considered pathogenic or likely pathogenic (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.

Review and reporting 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.

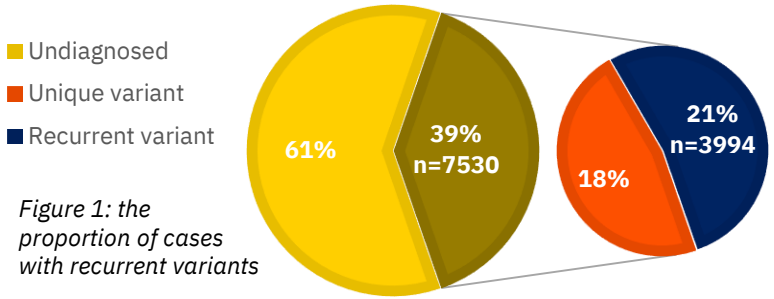


Figure 1: the proportion of cases with recurrent variants

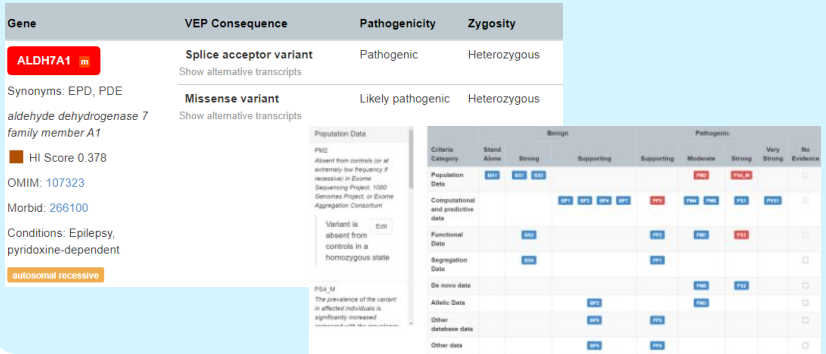
CONCLUSION

Automated classification and evidencing of previously reported variants could **save up to 85 minutes per case**, with the added benefits of **standardizing interpretation** between users and **reducing turnaround**, particularly in time-critical cases. Results are available to perform a manual second-check and sign-off prior to reporting to ensure clinical-grade results, without the additional need to repeatedly retrieve supporting data and manually assign ACMG criteria. **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 because she had **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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