Using Artificial Intelligence for Detection of Hotspot Regions: ACMG/AMP PM1 Criterion

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ABSTRACT

Background: The 2015 ACMG/AMP sequence variant interpretation guidelines provided a framework for classifying variants based on several benign (B) and pathogenic (P) evidence criteria, including a recent regulatory criterion for missense variants located in a hotspot region (PM1). Recently published recommendations called for increased standardization of, and more conservative, scoring for calling the PS1 rule for LOF variants. Here, we benchmarked the aiVCE’s ability to apply the PM1 rule for LOF variants.

Methods: Within the aiVCE, for each exon/domain, a sliding window first extracts candidate regions between each pair of B variants or at the edges of the region, in order for it to be clear of B variants. Candidate regions without P variants within them are ignored. Within each candidate region, the AI model further detects the inner borders of P variants contained within, and the number of P variants. Based on the density and number of P variants, the model evaluates each region for the presence of a hotspot and then assigns a weight to the PM1 rule as supporting, moderate, or strong. The AI-based weighting algorithm differentiates between the inner P region and the region between the P and B variants. In the absence of a gold standard for hotspot regions, we benchmarked the aiVCE’s ability to detect hotspot regions against the different gene/disease-specific expert panels’ (EP’s) recommendations for PM1 and their published curated variant datasets.

Results: Among the 131 variants where the aiVCE applied the PM1 rule, 110 (83.9%) were classified as B/LB or P/LP by the EPs. Of the 56 variants that were called as P/LP by the EPs, and for which the PM1 rule was met, 71% were classified as PM1 by the aiVCE.

Conclusion: We herein demonstrate AI-based algorithms can aid in the detection of exonic and domain hotspot locations in genes. This is due to the lack of gold standard databases for applying PM1 rule. An AI-based hotspot detection is highly desirable. Our results show that the identification of the hotspot was consistent with the final classification of a variant by the Expert Panels. As such, it can be valuable tool for making future investigations of gene-based variant classification.

Methods

Detection of Hotspot Regions (ACMG/AMP PM1 Criterion) using aiVCE

Within the aiVCE, for each exon/domain, a sliding window initially extracts candidate regions between each pair of B variants or at the edges of the region, in order for it to be clear of B variants. Candidate regions without P variants within them are ignored. Within each candidate region, the AI model further detects the inner borders of P variants contained within, and the number of P variants. Based on the density and number of P variants, the model evaluates each region for the presence of a hotspot and then assigns a weight to the PM1 rule as supporting, moderate, or strong. The AI-based weighting algorithm differentiates between the inner P region and the region between the P and B variants. In the absence of a gold standard for hotspot regions, we benchmarked the aiVCE’s ability to detect hotspot regions against the different gene/disease-specific expert panels’ recommendations for PM1 and their published curated variant datasets.

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Table 1. Clingen EPs’ gene/disease-especific published curated variant datasets utilized for assessing the aiVCE’s ability to detect hotspot regions

Table 2. Assessment of aiVCE ability to detect hotspot regions using Clingen EP recommendations for PM1 gene datasets

References

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