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Enabling genomic medicine

AI-enabled diagnosis for *KCNH1* epilepsy case with Congenica

Sadly, many people suffer from epilepsy and developmental delays, which presents many challenges for both individual patients and their families. According to the WHO, there are more than 50 million people worldwide with epilepsy – and an estimated 70% could be seizure free with the right medication. An early diagnosis can help clinicians prescribe the right medication and in turn prevent seizures from damaging the brain. In our blog series on clinical cases, we share examples of how Congenica enables and accelerates diagnosis and helps maximize the chances of identifying causal variants. Here is how the Congenica Clinical Consultancy Services (CCS) team helped with the genetic diagnosis of a *KCNH1* epilepsy case.

Clinical background

The case presented here concerns a young male patient with myoclonic epilepsy, generalized tonic-clonic seizures and developmental delay. An exome analysis of the patient's DNA was performed using the Congenica clinical decision support (CDS) platform.

In a singleton case such as this where there is no parental data to help narrow down the number of variants to review, one of the biggest challenges to the process of interpretation is the number of genes associated with epilepsy – a number that continues to grow over time. Using a virtual panel-based approach helps identify the most relevant candidate variants for review, narrowing the focus to variants in genes with the strongest clinical evidence. Such an approach also helps mask potential incidental findings.

For the original analysis, the clinical team used a virtual Epilepsy panel that was based on the Genomics England PanelApp Genetic epilepsy syndromes (high evidence) panel. However, the panel-focused analysis came back showing the patient had no variants within the set of epilepsy genes that would explain his clinical phenotype.

AI's role and impact

Later, following the introduction of Congenica AI to the CDS platform, the case was re-run by the Congenica CCS team and a variant in a gene called *KCNH1* was identified that warranted further investigation. Congenica AI uses artificial intelligence (AI) and machine learning to rank variants according to their relevance to the patient's phenotypes and likely pathogenicity. It is not limited to considering variants within a set of genes in a given virtual gene panel. As a result, it opens up the possibility of performing a broader analysis, without overwhelming the analyst with potentially hundreds or thousands of variants to review – helping to focus on the variants that matter the most.

This detected *KCNH1* variant has historically been reported in two syndromes (Temple-Baraitser syndrome and Zimmermann-Laband syndrome-1) that can present with epilepsy as a symptom. However, both syndromes have clinically recognisable phenotypes and epilepsy, if present, is not one of the main distinctive features. At the time of the original analysis in 2020, *KCNH1* was not known to cause epilepsy as an isolated phenotype and hence the gene was not part of the virtual gene panel and this variant was not identified.

Figure 1. *KCNH1 variant presents as the top-ranked variant.*

A publication in January 2021 subsequently identified variants in the *KCNH1* gene as causing a broad spectrum of epilepsy-related disorders, including in the absence of additional syndromic phenotypes [1]. This gene was reviewed by a Genomics England Curator in April 2021 who suggested an elevation from amber (moderate confidence) to green (high confidence) in the PanelApp Genetic epilepsy syndromes. However, as of the date of this case study, the panel has yet to be updated to reflect this evidence - the *KCNH1* gene remains as an amber gene. This illustrates how challenging it is for even gold standard curated panels to keep up with the published literature and in this case simply re-running the case using the high evidence virtual epilepsy panel would not have changed the outcome. Congenica AI, which considers and ranks all genes and variants, immediately identified the *KCNH1* variant as the top candidate (see Figure 1). The variant received a high confidence score (4.31 out of 5) based on multiple lines of evidence, supporting pathogenicity. Congenica AI also assessed the variant as causing a full contribution to the patient's primary phenotypes (seizures and global developmental delay), as well as partial contribution to the extended phenotypes (see Figure 2). Based on the evidence provided, the variant was determined to be the likely cause of the patient's condition.

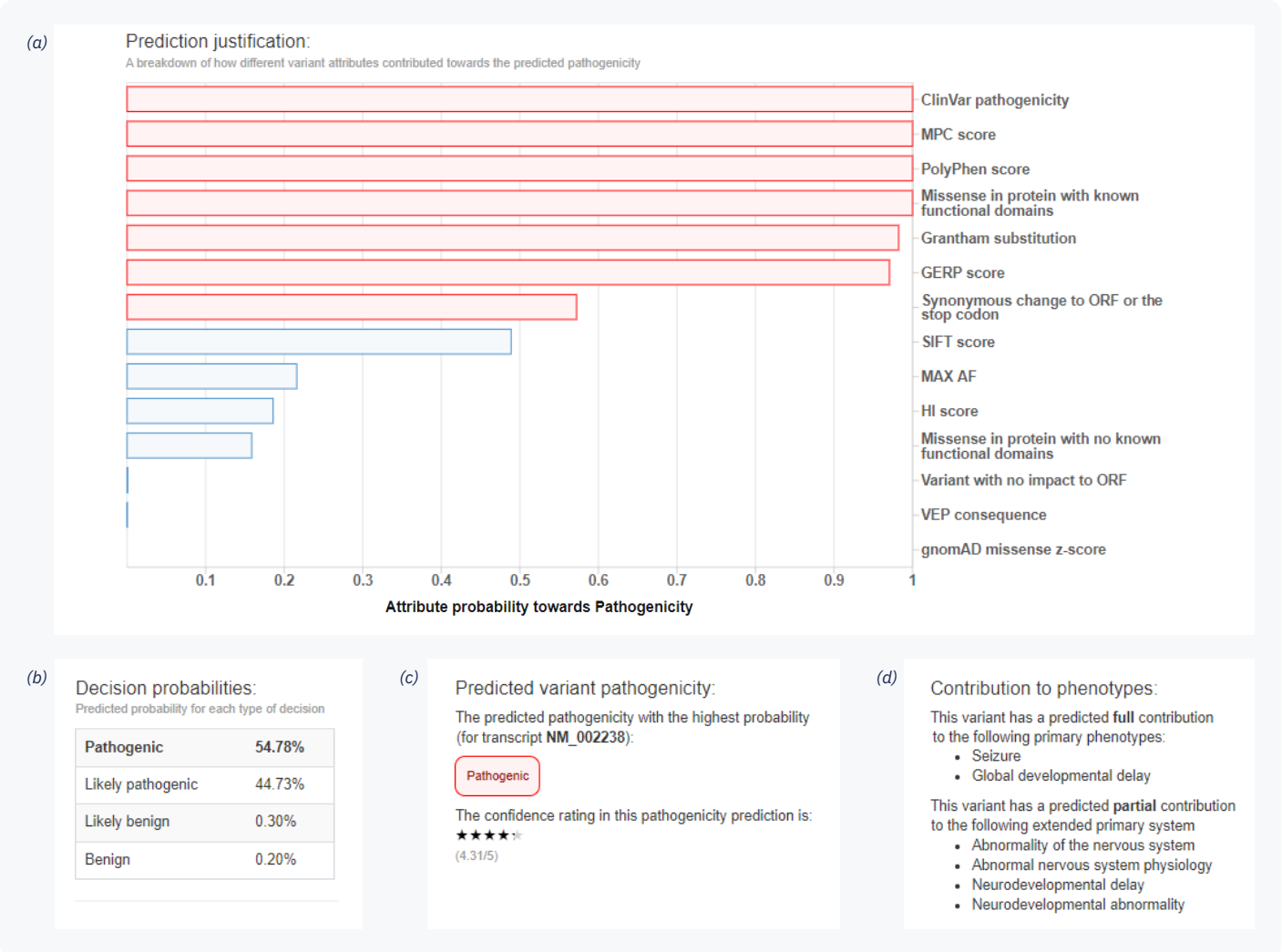

Figure 2. *Supporting evidence for KCNH1 variant ranking.* ***(a)*** *Display of variant attributes contributing to the variant's predicted pathogenicity.* ***(b)*** *Displayed calculation of the predicted probability for possible classification decisions.* ***(c)*** *Display of predicted variant pathogenicity and confidence rating.* ***(d)*** *Display of contribution to phenotypes.*

What does this diagnosis mean for the patient and his family?

Psychologically, it was a relief for the family to know what was causing their child's condition. The findings provide the opportunity for clinicians to offer parental testing to determine if the variant has arisen *de novo*. These results could help with reproductive decisions – if the variant is *de novo* then the recurrence risk of this variant is extremely low and future offspring are unlikely to be affected. Unfortunately, parental testing has not yet been performed in this family due to difficulties obtaining a sample from the father. This family is due to be followed-up by the clinical genetics team and this finding will enable them to assess potential changes to medication and possibly provide a more accurate prognosis for the future.

Some diagnoses are only possible with AI support

This case is a convincing example of how the Congenica CCS team used Congenica AI to discover a variant in a gene that would not have been identified using the typical, virtual gene-panel approach for a singleton.

Artificial intelligence is extremely useful in enabling faster analysis and increasing diagnostic yield due to its ability to consider and reliably rank all variants across all genes. This is particularly important in singleton cases where inheritance data from parental samples is not available to help narrow down the set of variants to be reviewed. AI enables more thorough interrogation of cases while presenting analysts with a small number of high-ranking variants for review.

Summary

This case was originally reported as negative because a phenotype-specific, virtual gene panel was used, which did not include *KCNH1* as a high-confidence epilepsy gene. With the introduction of Congenica AI to the CDS platform the data was re-analyzed by the Congenica CCS team. The *KCNH1* variant was identified as the top-ranked candidate based on the evidence for pathogenicity and contribution to phenotype and was determined to be a good fit based on the clinical picture and a recent publication. Using AI, the Congenica CCS team has provided a potentially life-improving diagnosis for this patient.

Clinical Case Key Fact Summary

- Test performed: singleton exome
- HPO terms used: seizure, global developmental delay
- Gene panel selected: none
- **Gene: KCNH1**
  - Temple-Baraitser syndrome / OMIM 611816 / AD
  - Zimmermann-Laband syndrome 1 / OMIM 135500 / AD
- **VARIANT:** c.1070G>A p.(Arg357Gln)
- **ACMG criteria, Evidence for reporting Likely Pathogenic**
  - PM2 - absent from gnomAD
  - PS4 - DECIPHER: 259697 and 274588, ClinVar: 279981
  - PM5 - p.Arg357Pro change in PMID 26818738 would have PM2, PM1, PM5, PP3 and PP2 applied for a LP classification
  - PP3
  - PM1 - missense constrained, hotspot mutation for LP/P variants in ClinVar. Located in the voltage-sensing S4 domain
  - PP2 - this gene is missense constrained and pathogenic missense variants are described in ClinVar
  - PS2 – de novo cases reported in the literature and DECIPHER
- **ADDITIONAL INFO:** ClinVar 2* Pathogenic/Likely pathogenic

References

1. Novel KCNH1 Mutations Associated with Epilepsy: Broadening the Phenotypic Spectrum of KCNH1-Associated Diseases. Von Rede et al. Genes (Basel). 2021 Jan 21;12(2):132.

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