EDITOR'S CHOICE ARTICLE

DECODING THE GENETIC ARCHITECTURE OF EPILEPSY USING GWAS

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INTRODUCTION

Given that epilepsy is a highly heritable condition influenced by both common and rare genetic variants, this study aimed to uncover the genetic architecture of epilepsy and explore how it varies across different subtypes. The research was a collaborative effort involving more than 200 researchers worldwide, conducted in association with the International League Against Epilepsy (ILAE), a non-profit organization dedicated to advancing epilepsy treatment through research and the education of physicians and policymakers.

METHODS & RESULTS

To uncover candidate loci, the study employed a genome-wide association study (GWAS), followed by further investigation to identify the underlying genes. The analysis included 29,944 cases, comprising 16,384 diagnosed with focal epilepsy (FE) and 7,407 with generalized epilepsy (GGE), the majority of which were of European descent. Genome data was partially sourced from biobank databases across various European and international regions.

GGE was found to have substantial genetic contributions from common variants, whereas FE showed minimal contributions from such variants, with no loci reaching genome-wide significance. Moreover, GGE-associated variants were enriched in genes expressed in excitatory and inhibitory neurons, suggesting a key role in intracellular signal transduction and synapse excitability. In contrast, non-inherited and polygenic genetic factors may play a more significant role in FE, with somatic mutations potentially being more prominent.

In all, 26 common epilepsy risk loci were identified, 16 of which were previously unknown. Further analysis revealed 29 genes potentially underlying these loci, many of which are already targets of widely prescribed medications, though not typically used for epilepsy (see Table 1). Notably, these medications could potentially be repurposed for epilepsy treatment, leading to new therapeutic modalities in the future. For example, CACNA2D2, a calcium channel gene, is a target of anti-seizure medications (gabapentin and pregabalin), as well as the Parkinson's disease drug safinamide and the nonsteroidal anti-inflammatory drug celecoxib. SCN8A, a sodium channel gene, is targeted by sodium-channel blocking drugs. RYR2, which has been linked to both cardiac disorders and epilepsy, is targeted by caffeine and statins. Finally, CHRM3, the acetylcholine receptor gene, is a target of solifenacin, a medication typically used for urinary incontinence.

DISCUSSION

Apart from uncovering 16 previously unknown common epilepsy risk loci, this study is significant because it provides a foundation for new epilepsy treatments. Many associated genes uncovered are already targets of established and widely prescribed medications, albeit used primarily for other conditions. Solifenacin and statins, although routinely used for urinary incontinence and lowering cholesterol respectively, could potentially

Table 1. Uncovered Epilepsy Risk Loci and Current Drugs Targeting Them

Receptor/Gene	Ion Permeability	Available Medications
CACNA2D2	Calcium (Ca2+)	gabapentin, pregabalin, safinamide, celecoxib
SCN8A	Sodium (Na+)	sodium-channel blockers, safinamide, quinidine
RYR2	Calcium (Ca2+)	caffeine, simvastatin, atorvastatin, carvedilol
CHRM3	Potassium (K+)	solifenacin

List of receptors/genes, ion permeability they are associated with and the available target medication based on source 1.

be repurposed as epilepsy treatments following the appropriate clinical trials confirming their effectiveness, leading to an acceleration of drug development for a disorder that has proved to be challenging to treat.

The primary limitations of this study are those shared by all research relying on GWAS – limited functional insight and missing rare variants. Although 29 genes underlying common epilepsy risk loci were identified, it is uncertain whether this association has any functional significance to the onset or progression of epilepsy. This hypothesis would need to be tested in controlled studies, possibly involving knockouts of the genes. Moreover, GWAS tends to be biased toward common variants. However, in the case of FE, rare variants are presumed to play a more significant role. Finally, a portion of the data came from biobanks, which rely on self-reported clinical information and hospital codes, which are prone to misclassification. Thus, the inclusion of such data, while it did significantly increase the size of the patient and control cohort, has also increased heterogeneity in epilepsy cohort studies and thus complicated genetic mapping.

CONCLUSION

This study uncovered marked differences in the genetic architecture underlying focal and generalized epilepsies, with the former being more associated with rare variants and somatic mutations and the latter often being associated with common risk variants. Moreover, it uncovered new common epilepsy risk genes whose function is already known and a target of long-used and widely prescribed medications, opening the way for future clinical trials and potentially accelerating epilepsy treatment through repurposed use of medication.

REFERENCES:

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