














RESEARCH ARTICLE

A pharmacogenomic assessment of psychiatric adverse drug reactions to levetiracetam

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Abstract

Objective: Levetiracetam (LEV) is an effective antiseizure medicine, but 10%–20% of people treated with LEV report psychiatric side-effects, and up to 1% may have psychotic episodes. Pharmacogenomic predictors of these adverse drug reactions (ADRs) have yet to be identified. We sought to determine the contribution of both common and rare genetic variation to psychiatric and behavioral ADRs associated with LEV.

Methods: This case-control study compared cases of LEV-associated behavioral disorder ($n = 149$) or psychotic reaction ($n = 37$) to LEV-exposed people with no history of psychiatric ADRs ($n = 920$). All samples were of European ancestry. We performed genome-wide association study (GWAS) analysis comparing those with LEV ADRs to controls. We estimated the polygenic risk scores (PRS) for schizophrenia and compared cases with LEV-associated psychotic reaction to controls. Rare variant burden analysis was performed using exome sequence data of cases with psychotic reactions ($n = 18$) and controls ($n = 122$).

Results: Univariate GWAS found no significant associations with either LEV-associated behavioural disorder or LEV-psychotic reaction. PRS analysis showed that cases of LEV-associated psychotic reaction had an increased PRS for schizophrenia relative to controls ($p = .0097$, estimate = .4886). The rare-variant analysis found no evidence of an increased burden of rare genetic variants in people who had experienced LEV-associated psychotic reaction relative to controls.

Significance: The polygenic burden for schizophrenia is a risk factor for LEV-associated psychotic reaction. To assess the clinical utility of PRS as a predictor, it should be tested in an independent and ideally prospective cohort. Larger sample sizes are required for the identification of significant univariate common genetic signals or rare genetic signals associated with psychiatric LEV ADRs.

KEYWORDS

adverse drug reactions, levetiracetam, pharmacogenomics, polygenic risk scoring, psychosis

1 | INTRODUCTION

Levetiracetam (LEV) is an effective antiseizure medicine (ASM), first licensed to treat epilepsy in 1999. Upon binding to its target, the synaptic vesicle protein SV2A, seizure activity is suppressed by LEV, which putatively modulates exocytosis from synaptic vesicles, thereby inhibiting pre-synaptic neurotransmitter release.^{1,2} As a first-prescription monotherapy, LEV can provide seizure freedom in over 50% of people with epilepsy.^{3,4} Adjunctive LEV treatment stopped focal and generalized seizures, which were previously drug resistant.^{5–7} LEV is commonly used for both monotherapy and polytherapy to treat a broad spectrum of seizure types.^{8,9}

Adverse drug reactions (ADRs) are associated with LEV treatment. An estimated 18% of people with epilepsy treated with LEV will experience some neuropsychiatric

Key points

- Polygenic risk scores for schizophrenia are predictive of levetiracetam (LEV)-induced psychotic reactions
- GWAS analysis reveals no clinically actionable common genetic variants for LEV behavioral or psychiatric adverse drug reactions
- Exome analysis identified no burden of rare variants in schizophrenia-associated genes, or LEV-target SV2A associated with LEV-induced psychotic reaction

response, resulting in dosage lowering or, more frequently, cessation of treatment.¹⁰ LEV-associated ADRs cover many phenotypes, including behavioral disorders such as

irritability and personality change and affective disorders such as depression and suicidal ideation. Furthermore, ~1% of people exposed to LEV will experience drug-induced psychotic reactions, a significantly higher rate than associated with other ASMs.^{10,11} As a group, psychiatric and behavioral side effects have the highest economic burden of all ASM-related ADRs.¹²

Previous pharmacogenomic research into ASM-associated ADRs, primarily focused on univariate analyses, has identified several clinically important predictors of clinical relevance. For example, human leukocyte antigen (HLA) region alleles HLA-B*15:02 and HLA-A*31:01, as well as the cytochrome P450 (*CYP*)2C9 *3 allele are strong predictors of aromatic ASM-induced severe cutaneous adverse reactions.^{13–16} A previous effort, focused on a limited number of single nucleotide polymorphisms (SNPs), reported a correlation between LEV-induced psychiatric ADRs and genetic variation linked to dopaminergic activity.¹⁷ To date, there has been no genomic investigation of LEV psychiatric ADRs.

Polygenic risk scoring (PRS) is a method used to assess an individual's cumulative burden of common genetic variants associated with a disease or trait.¹⁸ The predictive potential of PRS in the field of pharmacogenomics has been demonstrated previously. For example, people with bipolar disorder who have a higher PRS for schizophrenia were shown to be less likely to respond to mood-stabilization treatment with lithium.¹⁹ PRS for non-melanoma skin cancer has been shown to predict the risk of and time to azathioprine-associated post-transplant skin cancer.²⁰

The role of rare genetic variation in pharmacogenomics is less well assessed. Rare genetic variants in the *SLCO1B1* gene seem to influence the clearance of methotrexate, a chemotherapeutic agent.²¹ Rare variation in the *CYP* genes *CYP3A4* and *CYP2C9* appears to explain the 18.4% and 43.1% spectrum of enzyme activity.²² Bioinformatic predictions of the contribution of rare variation to drug metabolism suggest that rare variants may account for a substantial proportion of inter-individual variability of the metabolism of drugs such as warfarin and the statin medication simvastatin.²³

We utilized a variety of approaches to assess the role of genetic variation in psychiatric and behavioral ADRs associated with LEV. First, we applied a univariate genome-wide association study (GWAS) approach to identify individual common genetic risk loci for LEV-induced behavioral ADRs or LEV-associated psychotic reaction. We then applied a polygenic approach, using PRS to test whether a higher polygenic burden for schizophrenia can predict LEV-associated psychotic reactions. Finally, we performed burden analysis of exome data to identify if rare variants are associated with this clinical condition compared to controls.

2 | METHODS

All research participants (or their legal guardians in the case of minors or individuals with intellectual disability) provided written, informed consent. The study was approved by ethics committees at each study site.

2.1 | Cohort assembly

Genetic and phenotypic data on cases and controls were obtained from various recruitment sites. All cases and controls were people with epilepsy and a history of treatment with LEV.

EpiPGX Consortium samples were contributed from the following 10 sites:

The Royal College of Surgeons (Dublin, Ireland), Antwerp University Hospital (Belgium), Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) “G. Gaslini” Institute (Genova, Italy), the University of Liverpool (UK), the University of Tübingen (Germany), University Medical Centre, (Utrecht, The Netherlands), UCL Queen Square Institute of Neurology (UK), the University of Glasgow (UK), the University of Bonn (Germany), and the University of Melbourne (Australia).

We obtained additional cases (beyond EpiPGX) from the Beaumont Hospital Epilepsy Biobank (Dublin, Ireland), the Columbia University Medical Center (United States), and the Department of Medicine at the University of Melbourne, Austin Health (Australia).

2.2 | Case and control phenotyping

All phenotyping was conducted by the neurology team where the participant was recruited. To meet the criteria of an ADR, each case must have (1) occurred within 6 months of the initiation of LEV treatment, (2) led to withdrawal or dose reduction of LEV, (3) ADR reversed or improved after withdrawal or dose reduction, and (4) ADR not attributed to any other cause by the treating or phenotyping clinician.

We specifically examined two LEV ADR phenotypes:

- 1: Any LEV-induced behavioral disorder. Defined as one or more of the following: agitation, aggression, irritability, confusion, or cognitive decline.
- 2: LEV-induced psychotic reaction: vivid hallucinations, misidentifications, delusions and or ideas of reference (often of a paranoid or persecutory nature), psychomotor disturbances (excitement or stupor), and an abnormal affect, ranging from intense fear to ecstasy. The sensorium is usually clear, but some degree of clouding

of consciousness may be present, although not severe confusion. A psychiatrist must have confirmed the diagnosis. Any cases with a previous history of psychotic illness were excluded.

Controls were LEV-treated people with epilepsy with no psychiatric side-effects reported in clinical notes after a minimum of 6 months of treatment.

2.3 | Genotyping and quality control

EpiPGX samples were genotyped on various Illumina chips and underwent imputation and quality control (QC) processes, as reported previously.²⁴

The additional samples from Dublin (Beaumont) and Melbourne were genotyped on the Illumina Global Screening Array chip and imputed on the Sanger imputation server (<https://imputation.sanger.ac.uk/>) using the Haplotype Reference Consortium release 1.1 panel as a reference.²⁵ The newly genotyped samples underwent the same QC procedures as the EpiPGX cohort (see Ref. 24), and were then merged with the EpiPGX data set for further analysis.

To ensure European ancestry and genetic homogeneity all samples were merged with the Human Genome Diversity Project (HGDP).²⁶ Principal component analysis was conducted by thinning for linkage disequilibrium using PLINK 1.9 (--indep-pairwise 1000, 100, 0.1), and then estimating principal components (PCs). The top two PCs were graphed using R v3.5,²⁷ and any samples which did not overlay the European HGDP samples on the PCA plot were excluded.

2.4 | GWAS

We used the PGA2 software to estimate GWAS power,²⁸ based on a minimum minor allele frequency of 5% to detect an association to the alpha level of 5×10^{-8} under an additive model. GWAS analyses were carried out using a frequentist association model in SNPTEST,²⁹ with sex and the top six principal components included as covariates to account for bias and population stratification. The threshold for genome-wide significance was set at $p < 5 \times 10^{-8}$. We included only autosomal SNPs in our analyses.

2.5 | Polygenic risk scoring

Polygenic risk scores for schizophrenia were estimated for all samples with LEV-induced psychosis, and controls, using PRSice2.³⁰ GWAS results for schizophrenia were

obtained from the Psychiatric Genomics Consortium.³¹ All SNPs from the schizophrenia GWAS with p -values $\leq .5$ were included in the PRS analysis. PRS were normalized to mean 0 and SD 1 and then regressed onto LEV psychosis case: control status using R v3.5, with the top six PCs and sex included as covariates.

We used the pROC R package³² to estimate the area under the receiver-operating characteristic (ROC) curve of the above PRS model, compared to the null model, and a model comprising covariates only (PCs 1–6 and sex).

2.6 | Exome sequencing and analysis

Whole-exome sequencing was conducted at deCODE genetics on the Illumina HiSeq 2500 with the Nextera Rapid Capture Expanded Exome kit (Illumina). Adapter sequences were removed, and the data were put through a Genome Analysis Toolkit (GATK³³), best practices pipeline with the GRCh37 human reference genome³⁴ for joint calling, recalibration, filtering, and variant annotation. We excluded any variant position with a mean depth of less than 10 in all samples. Only samples with more than 30× mean coverage or more than 70% of the exome intervals covered by at least 20× mean coverage were included for analysis.

We first performed a hypothesis-free test single-gene collapsing analysis with the combined and multivariate collapsing (CMC) method with a two-sided Fisher exact test using rvtests.³⁵ We then performed gene set collapsing tests with the regression-based two-sided SKAT-O method,³⁶ testing for a burden of functional variants in genes that had been associated previously with schizophrenia (*SLC6A1*, *SETD1A*, *RBM12*³⁷). PCs 1–6 and sex were included as covariates.

3 | RESULTS

3.1 | Cohort description

We included 1106 people with epilepsy treated with LEV in our analysis, of which 149 had LEV-associated behavioral disorder, 37 had LEV-associated psychotic reaction, and 920 were controls. A full breakdown of case phenotypes and controls is provided in Table 1. Fifty-four percent of cases in our study were female, compared to 55% of controls. Cases had an average of 46, and controls an average age of 51, with an average age at first seizure of 17 for cases and 21 for controls. Twenty-seven percent of cases had generalized epilepsy, 59% had focal epilepsy, and 14% had unclassified epilepsy. Twenty-five percent of controls had generalized epilepsy, 67% had focal epilepsy, and 9%

were unclassified. Among cases, the most common EEG finding was generalized spike/wave discharges.

3.2 | Genome-wide association analyses of LEV-associated psychiatric ADRs

We conducted a GWAS of 149 cases with LEV-associated behavioral disorder vs 920 controls. After quality control, 3.8 million SNPs were included in the association analysis. Our analysis had 80% power to detect a genetic variant with a relative risk of 3.34 or greater. We did not observe any variants that surpassed the significance threshold of 5×10^{-8} (Figure 1A). The variant rs1800497, which had been reported previously to predict LEV-induced psychiatric ADRs,¹⁷ was found in our LEV-associated behavioral

disorder GWAS to have an uncorrected p -value of .458, although the phenotype criteria used in this study was not an exact match.

We next conducted a GWAS of LEV-induced psychotic reaction, which included 37 cases and 920 controls across 3.8 million SNPs. We estimated 80% power to detect a variant with a relative risk of 7.22 or greater. No genome-wide significant signals were observed (Figure 1B).

3.3 | Polygenic risk score analysis

We tested the hypothesis that people who experience LEV-induced psychotic reaction harbor an excess of common variants associated with schizophrenia using PRS analysis (see Methods). We found that the PRS for schizophrenia was significantly higher in LEV-psychotic reaction cases compared to controls (estimate = .4886, standard error [SE] = .1881, $p = .0097$). Schizophrenia PRS explained 4% of the phenotypic variance in case-control status. Generating a ROC curve of LEV-psychotic reaction case: control status from a model of schizophrenia PRS, PCs 1–6, and sex produced a curve with an area under the curve (AUC; predictive power) of 0.65 (Figure 2). This is greater than the AUCs of the null model (0.50) and a model built on covariates alone (0.57). LEV-psychosis cases make up 3.87% of our cohort (n cases = 37, n controls = 920; Table 1). If we take only samples in the top 10% of the schizophrenia PRS distribution, we find that

TABLE 1 Number of post-QC samples in each phenotypic group

ADR	Cases	Controls
LEV behavioral disorder	149	920
LEV psychotic reaction	37	920
LEV psychotic reaction (exome data)	18	122

Note: Also shown are the subset ($n = 18$) of patients with LEV-psychotic reaction ($n = 37$) who had exome data available.

Abbreviations: ADR, adverse drug reaction; LEV, levetiracetam; QC, quality control.

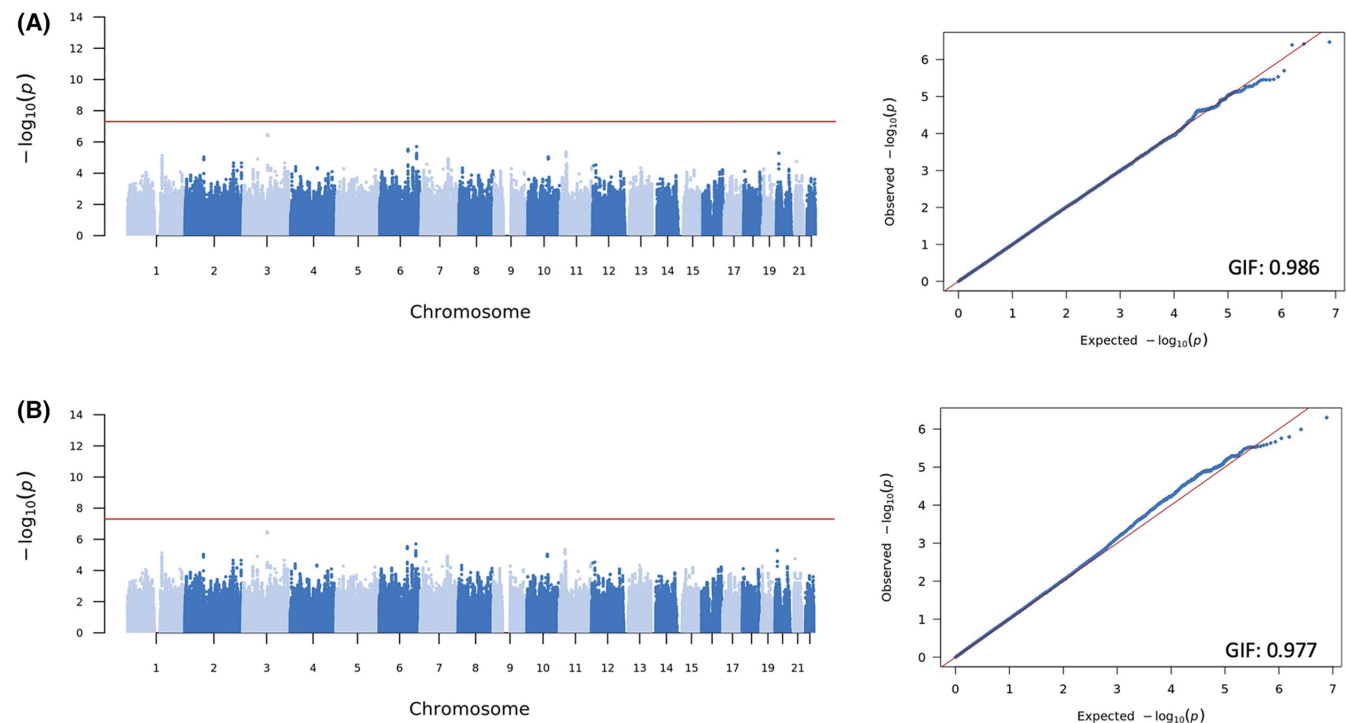


FIGURE 1 Manhattan plots (left), and quantile-quantile plots (right) for GWAS of (A) LEV-induced behavioural disorder and (B) LEV-induced psychosis. Genomic inflation factors displayed as GIF in the QQ plots. LEV, levetiracetam

LEV-psychosis cases make up 8.3% of the cohort (n cases = 8, n controls = 88). The bottom 10% of the schizophrenia PRS distribution contains only 1% LEV-psychosis cases (n cases = 1, n controls = 99).

3.4 | Rare variant burden analysis

To test the hypothesis that rare variant burden can contribute to the LEV-psychotic reaction, we performed rare variant analysis on people with LEV-induced psychotic reaction. First, all genes were tested individually for the enrichment of variation. After Bonferroni correction for 18 668 protein-coding genes, no gene reached the threshold of statistical significance ($p < 2.67^{-6}$). We tested for rare variant burden in genes previously found to harbor rare variants in people with schizophrenia. We found no significant enrichment of rare variation in *SLC6A1* ($p = .819$), *SETD1A* ($p = .030$), or *RBM12* ($p = .220$), given a threshold of statistical significance of $p < .016$. Testing rare-variant burden in these schizophrenia-associated genes together as a unit also found no significant enrichment ($p = .83$). We did not observe a burden of rare variants in the target of LEV *SV2A* ($p = .492$).

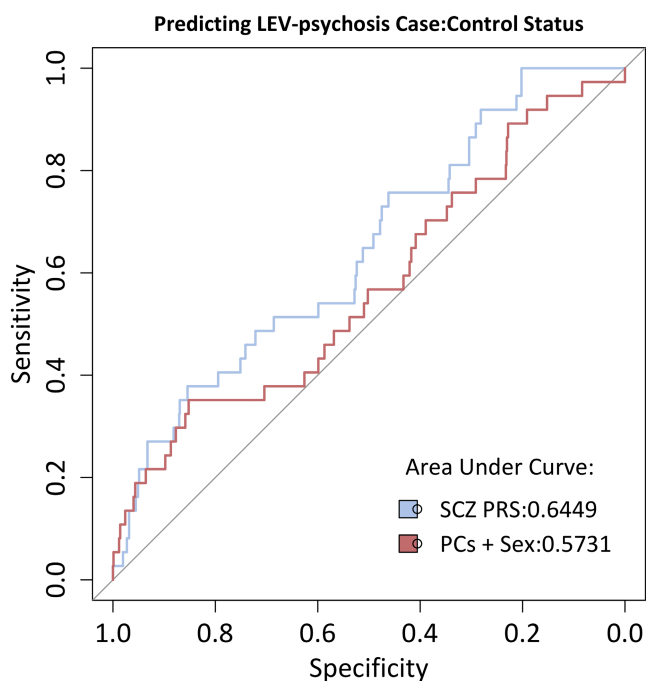


FIGURE 2 Area under the receiver-operating characteristic curve for LEV-psychotic reaction PRS analysis. The red line shows a model built from covariates only (PCs 1–6 + sex), the blue line is a model of both covariates and schizophrenia PRS. LEV, levetiracetam; PRS, polygenic risk score

4 | DISCUSSION

Levetiracetam (or LEV) is a highly effective ASM that is associated with behavioral adverse events in a proportion of patients, including affective disorder, aggression, and psychotic reactions.³⁸ We applied various analytical models to assess the role of genetic variation in LEV behavioral ADRs. We present evidence that the genetic burden for schizophrenia, as quantified by PRS, is a risk factor for LEV-induced psychotic reactions in people with epilepsy. We found no evidence of rare variant burden in LEV psychosis. From univariate GWAS analysis, we can conclude that there are no common variants with an OR >7.22 associated with LEV-induced psychotic reaction, or an OR >3.34 associated with an LEV behavioral disorder.

We then constructed a predictive model for LEV-psychotic reaction using schizophrenia PRS with a predictive power (as measured by AUC/ROC analysis) of 65%. This model explained 4% of the variation in case: control status for LEV psychosis in our cohort. The schizophrenia GWAS used to estimate the PRS explained 7% of the variation in schizophrenia case: control status, representing the upper limit of phenotypic variation that could be explained by a PRS model generated from it.³¹ More powerful GWAS of schizophrenia that explains more phenotypic variation may allow more accurate PRS models in the future.

These results raise the possibility of screening people with epilepsy to identify those at risk of developing psychotic reactions as an ADR, before exposure to LEV. Our findings must be validated in an independent sample ideally collected in a prospective study to clarify clinical potential.

The ability to screen for individuals at risk of developing LEV-induced psychotic reactions could be improved by including known clinical risk factors such as a history of depression or anxiety or a history of recreational drug use.³⁹ Given that LEV is a commonly prescribed first-line ASM,⁴⁰ and that up to 18% of people prescribed LEV will experience some side effects,⁴¹ identifying those at risk of ADRs would appear clinically attractive.

Our study has limitations. First, we focused on people of European ancestry. Given that PRS effects cannot be assumed to act consistently across ethnic backgrounds, the role of schizophrenia PRS in non-European LEV-psychosis cases must be assessed separately.⁴² Second, the relatively low number of cases included in our analyses limited our power to detect effects, particularly in the case of the rare variant analysis. Finally, although the potential dose/concentration-dependent LEV-induced psychosis could not be explored in this study, clinicians could consider optimizing therapeutic LEV treatment in the patients.

In summary, we showed that polygenic burden for schizophrenia is a risk factor for LEV-induced psychotic reactions. To assess the clinical utility of this result, it should

be tested in an independent and ideally prospective cohort. The following steps would include testing larger cohorts for univariate GWAS signals and further exome analysis in larger samples to assess the rare variant contribution to LEV psychiatric ADRs. Future research could also perform similar genetic analysis on other ASMs that are known to associate with behavioral and/or psychiatric ADRs.

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CONFLICT OF INTEREST

The authors have no financial conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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