

Polygenic burden in focal and generalized epilepsies

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Rare genetic variants can cause epilepsy, and genetic testing has been widely adopted for severe, paediatric-onset epilepsies. The phenotypic consequences of common genetic risk burden for epilepsies and their potential future clinical applications have not yet been determined. Using polygenic risk scores (PRS) from a European-ancestry genome-wide association study in generalized and focal epilepsy, we quantified common genetic burden in patients with generalized epilepsy (GE-PRS) or focal epilepsy (FE-PRS) from two independent non-Finnish European cohorts (Epi25 Consortium, $n = 5705$; Cleveland Clinic Epilepsy Center, $n = 620$; both compared to 20 435 controls). One Finnish-ancestry population isolate (Finnish-ancestry Epi25, $n = 449$; compared to 1559 controls), two European-ancestry biobanks (UK Biobank, $n = 383\,656$; Vanderbilt biorepository, $n = 49\,494$), and one Japanese-ancestry biobank (BioBank Japan, $n = 168\,680$) were used for additional replications. Across 8386 patients with epilepsy and 622 212 population controls, we found and replicated significantly higher GE-PRS in patients with generalized epilepsy of European-ancestry compared to patients with focal epilepsy (Epi25: $P = 1.64 \times 10^{-15}$; Cleveland: $P = 2.85 \times 10^{-4}$; Finnish-ancestry Epi25: $P = 1.80 \times 10^{-4}$) or population controls (Epi25: $P = 2.35 \times 10^{-70}$; Cleveland: $P = 1.43 \times 10^{-7}$; Finnish-ancestry Epi25: $P = 3.11 \times 10^{-4}$; UK Biobank and Vanderbilt biorepository meta-analysis: $P = 7.99 \times 10^{-4}$). FE-PRS were significantly higher in patients with focal epilepsy compared to controls in the non-Finnish, non-biobank cohorts (Epi25: $P = 5.74 \times 10^{-19}$; Cleveland: $P = 1.69 \times 10^{-6}$). European ancestry-derived PRS did not predict generalized epilepsy or focal epilepsy in Japanese-ancestry individuals. Finally, we observed a significant 4.6-fold and a 4.5-fold enrichment of patients with generalized epilepsy compared to controls in the top 0.5% highest GE-PRS of the two non-Finnish European cohorts (Epi25: $P = 2.60 \times 10^{-15}$; Cleveland: $P = 1.39 \times 10^{-2}$). We conclude that common variant risk associated with epilepsy is significantly enriched in multiple cohorts of patients with epilepsy compared to controls—in particular for generalized epilepsy. As sample sizes and PRS accuracy continue to increase with further common variant discovery, PRS could complement established clinical biomarkers and augment genetic testing for patient classification, comorbidity research, and potentially targeted treatment.

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Abbreviations: FE = focal epilepsy; GE = generalized epilepsy; GWAS = genome-wide association study; PRS = polygenic risk score

Introduction

Epilepsy is a common chronic neurological disorder, affecting approximately 1% of individuals (Ngugi *et al.*, 2010). Lifetime prevalence is 8–10% for a seizure and 3–4% for epilepsy (Hesdorffer *et al.*, 2011). The median incidence of epilepsy is 50 per 100 000 person-years (Ngugi *et al.*, 2011). Individuals at high risk for recurrent seizures (epilepsy) benefit from early antiseizure drug treatment, compared to no treatment or delayed treatment (Kim *et al.*, 2006). Predicting whether an individual will develop epilepsy after the first epileptic seizure is difficult (MacDonald *et al.*, 2000; Bell *et al.*, 2016), with recurrence risk varying from 27% to 71% (Hopkins *et al.*, 1988; Berg and Shinnar, 1991; Kwan and Sander, 2004).

Epileptic seizures either have a generalized (involving both cerebral hemispheres) or a focal (originating from one cerebral hemisphere) onset (Scheffer *et al.*, 2017). Generalized epilepsies account on average for 54%, focal epilepsies for 40%, and unclassifiable epilepsies for 7% of incident epilepsies in population-based studies of all ages (Banerjee *et al.*, 2009). Distinguishing between the two types of epilepsy can be difficult: focal epilepsy can present with bilateral tonic-clonic seizures (secondary-generalization), patients with generalized epilepsy can have focal features on EEG (Japaridze *et al.*, 2016), and some individuals have a mix of focal and generalized epilepsy (Scheffer *et al.*, 2017). Since commonly used antiseizure drugs for focal epilepsy can be ineffective or exacerbate generalized epilepsies, differentiating between focal and generalized epilepsy is important (Japaridze *et al.*, 2016). Hence, there is a clinical need for biomarkers that can help to distinguish

individuals at high versus low risk to develop either focal or generalized epilepsy.

Genetic factors can explain a substantial portion of cases of epilepsy, particularly severe epilepsy (EpiPM Consortium *et al.*, 2015). For rare and early onset childhood epilepsies, >100 epilepsy-related genes have been discovered in recent years (Heyne *et al.*, 2019). The identified genetic variants are rare and of large effect, ranging from large deletions that confer on average ~7-fold risk for epilepsy (Pérez-Palma *et al.*, 2017) to single, causative *de novo* variants in >33 genes (Heyne *et al.*, 2018). These variants are diagnostically relevant and can influence patient management. For example, treatment with sodium channel blockers can exacerbate seizures in patients with Dravet syndrome or other early-onset epileptic syndromes caused by *SCN1A* mutations, whereas these drugs are beneficial in patients with gain-of-function variants in *SCN2A* (Guerrini *et al.*, 1998; Löscher, 2009; Wolff *et al.*, 2017). While rare variation of large effect has a clear impact in clinical practice for rare epilepsy syndromes (McTague *et al.*, 2016), patients affected by common types of epilepsy rarely carry such variants and routine genetic testing is therefore not established for the common epilepsies.

Genome-wide association studies (GWAS) for common forms of epilepsy have identified common genetic risk variants for generalized epilepsy, focal epilepsy, and febrile seizures (Kasperavičiūtė *et al.*, 2013; Feenstra *et al.*, 2014; International League Against Epilepsy Consortium on Complex Epilepsies, 2014, 2018). Common genetic risk variants associated with a disease are usually of small effect size (1.33 median odds ratio) (Hindorff *et al.*, 2009) and cannot individually quantify risk or to inform

prognosis and treatment. However, polygenic risk scores (PRSs) that combine the effect sizes of thousands of variants into a single score can stratify affected and healthy individuals. For five common disorders, a recent study showed a 3- to 5-fold increased risk for patients with a high disease-specific PRS, similar to the range of risk conferred by rare monogenic variants, such as *LDLR* missense variants for coronary artery disease or rare *BRCA* variants in breast cancer (Khera *et al.*, 2018). Based on these results, the authors proposed that PRS-based prediction may be reliable enough to consider their utility in clinical practice.

Genome-wide PRS based on thousands of common variants associated with epilepsy may help distinguish healthy individuals from those who develop epilepsy (Speed *et al.*, 2014). However, no studies have directly investigated whether PRSs derived from well-phenotyped cohorts stratify patients in clinical practice or population-based cohort studies. Here, we calculate PRSs for the two main subtypes of epilepsy (generalized and focal) from the largest GWAS in epilepsy to date (International League Against Epilepsy Consortium on Complex Epilepsies, 2018) and (i) quantify the burden of PRSs derived from GWAS studies of well-phenotyped cohorts in patients with generalized or focal epilepsy; (ii) explore if PRS can differentiate patients with generalized from those with focal epilepsy; and (iii) explore if patients with generalized or focal epilepsy are enriched particularly in the upper extreme of the PRS burden distribution compared to controls. Our overall study design is presented in Fig. 1. Across two independent research cohorts, one clinically ascertained cohort, and three biobanks (repositories with clinical data and DNA samples available for research); data from 630 598 individuals were available for the PRS analyses.

Patients and methods

Study cohorts

Patients of European ancestry with generalized epilepsy or focal epilepsy were recruited through the Epi25 project (<http://epi-25.org/>), an international multicentre epilepsy genetics research consortium [exploration cohorts for generalized (GE) and focal (FE) epilepsy: GE-Epi25-EUR and FE-Epi25-EUR, respectively] and from a single clinical centre, the Cleveland Clinic Epilepsy Center (replication cohorts for generalized and focal epilepsy: GE-Cleveland-EUR and FE-Cleveland-EUR, respectively). A Finnish-ancestry population isolate was recruited from the Epi25 project (GE-Epi25-FIN and FE-Epi25-FIN, respectively). Ancestry-matched population controls were recruited from several in-house projects, the Partners HealthCare Biobank (Karlson *et al.*, 2016), and the FINRISK study (Borodulin *et al.*, 2017). Three large-scale biobank repositories [UKB: UK Biobank (Sudlow *et al.*, 2015); BioVU: Vanderbilt University biorepository (Roden *et al.*, 2008); and BBJ: BioBank Japan (Nagai *et al.*, 2017)] were used for additional explorations. All cohorts, totalling 630 598 individuals, are detailed in Table 1 and the Supplementary material.

Polygenic risk scoring in the study cohorts

Single-nucleotide polymorphism (SNP) weights for PRS were derived from summary statistics of the ILAE Consortium on Complex Epilepsies GWAS for generalized and focal epilepsy (International League Against Epilepsy Consortium on Complex Epilepsies, 2018). SNP weights for negative control PRS were derived from the UKB GWAS for type 2 diabetes for all cohorts excluding the UKB, and from the DIAGRAM-type 2 diabetes GWAS (Scott *et al.*, 2017) for the UKB. PRS for each individual were generated using the allelic scoring function, as implemented in PLINK v1.9 (Chang *et al.*, 2015). Individual PRSs were calculated as the sum of weighted effect alleles divided by the number of SNPs in the analysis. We generated the PRSs at the *P*-value threshold 0.5, found to be the best predicting threshold in a random split (80% training, 20% validation) of our exploration cohort (Epi25-EUR, Supplementary material 4.8, Supplementary Tables 4 and 5). We excluded individuals if their data were included in the GWAS studies used for PRS development. Details of the method to detect overlapping individuals across cohorts and the SNP quality control applied are given in the Supplementary material.

Statistical analysis

We used logistic regression adjusted for sex and for the first four principal components of ancestry to determine the ability of PRS to stratify cases from controls. The proportion of phenotypic variance explained by PRS was calculated using Nagelkerke's pseudo- R^2 , by comparing the full model of the logistic regression (PRS plus all covariates: sex and the first four principal components of ancestry) to the null model (covariates only). Following the example of Khera *et al.* (2018) we assessed the enrichment of the two epilepsy phenotypes (generalized epilepsy or focal epilepsy) in progressively more extreme tails of the PRS distribution (top 20%, 5%, 0.5%) against the remainder of the distribution in a logistic regression model predicting disease status, adjusted for sex and the first four principal components of ancestry. The threshold for statistical significance after Bonferroni correction was set to $\alpha = 1.67 \times 10^{-2}$ (three tests per cohort). Fixed-effect meta-analysis, with adjustment for the effective sample size, was performed using METAL (Willer *et al.*, 2010).

Data availability

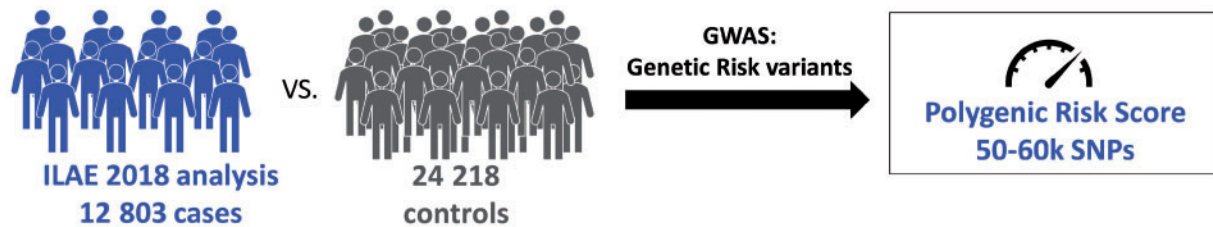
The data that support the findings of this study are available from the Epi25 Consortium, upon reasonable request. The biobank data are available from the UKB, BioVU, and BBJ upon successful project application.

Results

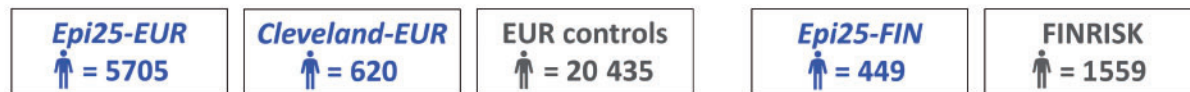
Higher PRS burden in patients with epilepsy compared to controls

To determine if common variants associated with epilepsy are enriched in independent cohorts of patients with

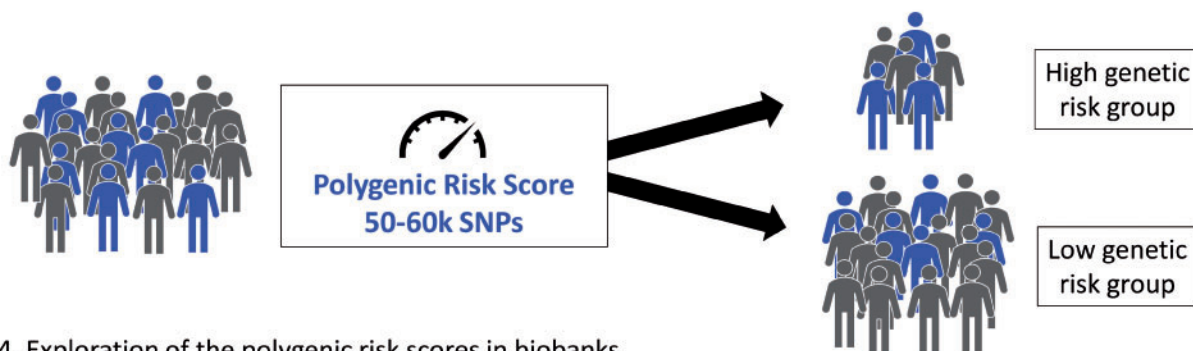
1. Genome-wide association study (GWAS) for risk score generation



2. Polygenic risk scoring in independent patient and matched control cohorts



3. Characterization of the polygenic risk score distributions in the combined case / control cohorts



4. Exploration of the polygenic risk scores in biobanks



Figure 1 Study design. (1) PRSs for the two main classes of epilepsy (generalized and focal) were derived from the largest GWAS in epilepsy to date (International League Against Epilepsy Consortium on Complex Epilepsies, 2018). (2) PRS were calculated in patients with generalized or focal epilepsy and in population controls and (3) tested in their ability to identify significant differences of common variant burden among groups. (4) The UK and Vanderbilt biobanks were available to test the behaviour of the PRSs in individuals ascertained by ICD-10 codes for epilepsy, while the Biobank Japan was available to test the performance in a non-European population. SNP = single nucleotide polymorphism.

Table 1 Study cohorts after quality control

Cohort name	Ascertainment type	Ethnicity	Generalized epilepsy (GE)	Focal epilepsy (FE)	Controls
Epi25-EUR	Research	EUR	2256	3449	20 435
Cleveland-EUR	Clinic	EUR	85	535	20 435
Epi25-FIN	Research	FIN	112	337	1559
UKB	Biobank	EUR	246	213	383 197
BioVU	Biobank	EUR	293	536	48 665
BBJ	Biobank	JPN	219	105	168 356

Generalized and focal epilepsy were diagnosed in the Epi25-EUR, Cleveland-EUR, Epi25-FIN, and BBJ cohorts according to clinical criteria (clinical interview, neurological examination, EEG, imaging data). For the UK and BioVU biobanks, ICD-10 G40.3 codes were used to identify people with generalized epilepsy, and G40.0 to G40.2 codes to identify people with focal epilepsy.

BBJ = BioBank Japan; BioVU = Vanderbilt University biorepository; Cleveland-EUR = European-ancestry Cleveland Clinic Epilepsy Center cohort; Epi25-EUR = European-ancestry Epi25 cohort; Epi25-FIN = Finnish-ancestry Epi25 cohort; UKB = UK Biobank.

generalized epilepsy or focal epilepsy compared to population controls, we conducted a PRS analysis in two independent epilepsy cohorts of European ancestry. We found that in the GE-Epi25-EUR cohort, genome-wide polygenic risk scores for generalized epilepsy (GE-PRS) were significantly higher in patients with generalized epilepsy ($n = 2256$ cases) than in population controls ($n = 20\,435$ controls; $P = 2.35 \times 10^{-70}$; Fig. 2 and Supplementary Table 1). GE-PRS explained 2.8% of the total phenotypic variance (composed of genetic, environmental, and genetic-environmental interaction variances) among the case and control group of the GE-Epi25-EUR cohort (Supplementary Table 1). This observation was replicated in the clinical GE-Cleveland-EUR cohort ($P = 1.43 \times 10^{-7}$; $n = 85$ cases; 2.6% phenotypic variance explained). In the FE-Epi25-EUR cohort, the genome-wide polygenic risk for focal epilepsy (FE-PRS) was significantly higher in patients with focal epilepsy ($n = 3449$ cases) than in population controls ($P = 5.74 \times 10^{-19}$), with 0.6% of the phenotypic variance explained. This observation was replicated in the clinical FE-Cleveland-EUR cohort ($n = 535$; $P = 1.69 \times 10^{-6}$; 0.5% phenotypic variance explained). As expected, PRSs for type 2 diabetes (negative control) were not significantly higher in patients with generalized epilepsy or focal epilepsy than in population controls (Fig. 2 and Supplementary Table 1).

To test the utility of PRSs across different populations, we investigated the power of the PRS derived from the European population in the isolated Finnish population. The GE-PRS was significantly higher in patients with generalized epilepsy ($n = 112$ cases) than in the population controls ($n = 1559$ controls; $P = 3.11 \times 10^{-4}$; Supplementary Fig. 2 and Supplementary Table 2). However, the PRSs explained less phenotypic variance than generalized epilepsy cohorts of European ancestry

(2% phenotypic variance explained). The FE-PRS were not significantly different between Finnish patients with focal epilepsy ($n = 337$ cases) and controls ($P = 0.55$).

Higher PRS burden in generalized compared to focal epilepsy

To determine if common variants associated with generalized epilepsy are enriched in patients with generalized epilepsy compared to patients with focal epilepsy, we regressed the GE-PRS against the diagnosis of generalized epilepsy or focal epilepsy. In the Epi25-EUR cohort, GE-PRSs were significantly higher in patients with generalized epilepsy than in those with focal epilepsy ($P = 1.64 \times 10^{-15}$), explaining 1.7% of the phenotypic variance (Supplementary Table 1). This observation was replicated in the Cleveland-EUR cohort ($P = 2.85 \times 10^{-4}$, 3.9% phenotypic variance explained) and the Epi25-FIN cohort ($P = 1.80 \times 10^{-4}$, 4.6% phenotypic variance explained, Supplementary Table 2). Overall, the PRS had the most predictive power in the corresponding epilepsy phenotype group: GE-status was best predicted by GE-PRS ($P = 2.35 \times 10^{-70}$, 2.8% phenotypic variance explained in Epi25-EUR) over FE-PRS ($P = 1.71 \times 10^{-15}$, 0.6% phenotypic variance explained) and FE-status was best predicted by FE-PRS ($P = 5.74 \times 10^{-19}$, 0.6% phenotypic variance explained in Epi25-EUR) over GE-PRS ($P = 8.21 \times 10^{-18}$, 0.5% phenotypic variance explained, Supplementary Table 1).

Enrichment of patients with epilepsy in the highest PRS burden percentile

To explore if the GE- and FE-PRS enrichment in patients with epilepsy is due to a few patients with a very high

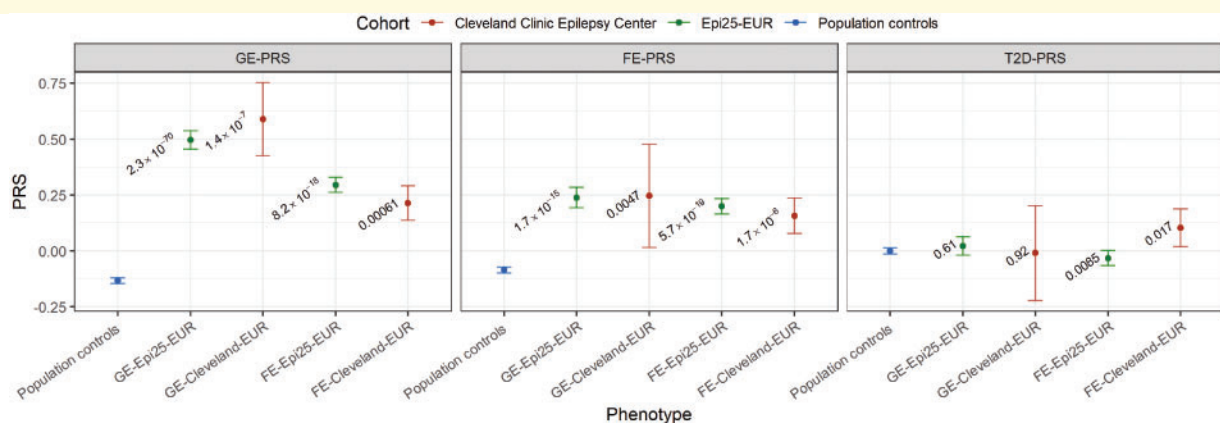


Figure 2 Genome-wide polygenic risk for generalized epilepsy or focal epilepsy in the exploration and replication cohorts.

Shown are the means of the standardized GE-, FE-, and type 2 diabetes-PRS with 95% confidence intervals for the European-ancestry population controls (highlighted in blue; $n = 20\,435$), the European-ancestry generalized epilepsy and focal epilepsy Epi25 exploration cohorts (highlighted in green; GE-Epi25-EUR, $n = 2256$; FE-Epi25-EUR, $n = 3449$), and the European-ancestry generalized epilepsy and focal epilepsy Cleveland Clinic replication cohorts (highlighted in red; GE-Cleveland-EUR, $n = 85$; FE-Cleveland-EUR, $n = 535$). The P -values for the differences between cases and population controls are given as numbers. The threshold for statistical significance after Bonferroni correction was set to $\alpha = 1.67 \times 10^{-2}$ (three tests per cohort).

burden or due to many with a slightly elevated burden, we characterized the epilepsy PRS distribution in the European-ancestry cohorts. Patients with epilepsy and population control subjects were ranked according to their PRSs and tested for enrichment of patients with generalized epilepsy or focal epilepsy in the extreme tails of the PRS distribution. Strikingly, in the combined GE-Epi25-EUR and control cohorts, we observed a significant 4.63-fold enrichment of patients with generalized epilepsy in the group with the highest GE-PRS (top 0.5%, $P = 2.60 \times 10^{-15}$; involving 2.39% of the GE-Epi25-EUR cohort; Table 2). This observation was replicated in the clinical GE-Cleveland-EUR cohort (4.47-fold enrichment; $P = 1.39 \times 10^{-2}$; 3.53% of the GE-Cleveland-EUR cohort). In the FE-Epi25-EUR cohort, we observed a significant 2-fold enrichment of patients with focal epilepsy in the group with the highest FE-PRS (top 0.5%, $P = 5.57 \times 10^{-4}$; 1.16% of the FE-Epi25-EUR cohort; Table 2). This observation was not replicated in the smaller clinical FE-Cleveland-EUR cohort ($P = 0.22$). All patients with top 0.5% highest PRS were found in the top decile of the GE- and FE-PRS distributions of the Epi25-EUR cohort (Supplementary Figs 3 and 4). Measures of the diagnostic accuracy of the PRS are given in Supplementary Table 8.

Epilepsy PRSs have limited value in biobank-derived cohorts based on ICD-10 codes

To evaluate whether common epilepsy variants identified in well-phenotyped patients are enriched in patient cohorts ascertained from patient registries and biobanks, we extended our GE- and FE-PRS analyses to include three

biobank-derived cohorts. In the UKB and BioVU biobanks, diagnosis was ascertained by ICD-10 codes for epilepsy and by a standardized questionnaire for the attending physicians in the BBJ biobank. Fixed-effect meta-analysis of the two European biobanks (UKB and BioVU), adjusted for the effective sample size (Willer *et al.*, 2010), revealed significantly higher GE-PRS in individuals coded as having generalized epilepsy than in population controls ($P = 7.99 \times 10^{-4}$, 539 patients with generalized epilepsy against 431 862 population controls). However, the PRS explained only very little of the phenotypic variance in each biobank (UKB: 0.12% variance explained; BioVU: 0.19%). In the BBJ, the GE-PRS were not significantly different between Japanese-ancestry patients with generalized epilepsy and controls ($P = 0.33$, 219 patients with generalized epilepsy against 168 356 controls). The FE-PRS were not significantly different between individuals coded as having focal epilepsy and controls in any of the three studied biobanks (UKB: $P = 0.44$; BioVU: $P = 0.23$; BBJ: $P = 0.29$). The PRSs for type 2 diabetes (negative control) were not significantly different in patients with generalized epilepsy or focal epilepsy than in population controls. The results in the three biobanks are detailed in Supplementary Table 3.

Discussion

We identified a significantly higher genetic burden for epilepsy, as quantified by PRS, in independent cohorts of patients with epilepsy as compared to population controls. While modest effect sizes preclude risk prediction based on single common genetic variants, PRSs that combine thousands of variants show predictive ability across a

Table 2 Enrichment of patients with epilepsy in the extreme tails of the PRS distribution

	Reference group	OR	95% CI	P-value	Cases/controls upper PRS%	Cases/controls lower PRS%	Sensitivity	Specificity
GE-PRS / GE-Epi25								
Top 20% of distribution	Remaining 80%	2.04	1.86–2.25	4.61×10^{-48}	887/3652	1369/16 783	0.393	0.821
Top 5% of distribution	Remaining 95%	2.39	2.06–2.76	4.39×10^{-32}	305/830	1951/19 605	0.135	0.959
Top 0.5% of distribution	Remaining 99.5%	4.63	3.16–6.76	2.60×10^{-15}	54/60	2202/20 375	0.024	0.997
GE-PRS / GE-Cleveland								
Top 20% of distribution	Remaining 80%	2.09	1.33–3.28	1.31×10^{-3}	35/4070	50/16 365	0.412	0.801
Top 5% of distribution	Remaining 95%	2.02	1.00–3.72	3.44×10^{-2}	11/1016	74/19 419	0.129	0.950
Top 0.5% of distribution	Remaining 99.5%	4.47	1.07–12.6	1.39×10^{-2}	3/100	82/20 335	0.035	0.995
FE-PRS / FE-Epi25								
Top 20% of distribution	Remaining 80%	1.35	1.24–1.48	2.32×10^{-11}	992/3785	2457/16 650	0.288	0.815
Top 5% of distribution	Remaining 95%	1.44	1.25–1.66	7.74×10^{-7}	292/903	3157/19 532	0.085	0.956
Top 0.5% of distribution	Remaining 99.5%	2.00	1.34–2.95	5.57×10^{-4}	40/80	3409/20 355	0.012	0.996
FE-PRS / FE-Cleveland								
Top 20% of distribution	Remaining 80%	1.49	1.22–1.82	1.04×10^{-4}	148/4047	387/16 388	0.277	0.802
Top 5% of distribution	Remaining 95%	1.55	1.09–2.14	1.17×10^{-2}	40/1009	495/19 426	0.075	0.951
Top 0.5% of distribution	Remaining 99.5%	1.83	0.62–4.32	0.22	5/100	530/20 335	0.009	0.995

Odds ratios (OR) and P-values were calculated by comparing those within the top 0.5, 5, and 20% of the PRS distribution, to the remainder of the PRS distribution in a logistic regression model adjusted for sex and the first four principal components of ancestry. The threshold for statistical significance after Bonferroni correction was set to $\alpha = 1.67 \times 10^{-2}$ (three tests per cohort). CI = confidence interval; EUR = European.

range of complex traits and diseases, including neuropsychiatric disorders (Khera *et al.*, 2018). In the setting of a collaborative epilepsy genetics community, we demonstrate that available datasets have reached an adequate size to address the role of common genetic variants, each with small effect sizes, in large populations of patients with epilepsy. In line with previous studies showing significant differences between the genetic architectures of generalized epilepsy and focal epilepsy (Speed *et al.*, 2014; International League Against Epilepsy Consortium on Complex Epilepsies, 2018), we also show that patients with generalized epilepsy have a significantly higher burden of common risk variants associated with generalized epilepsy than patients with focal epilepsy. The PRSs perform similarly in a multicentre research cohort and in an unselected—although much smaller—cohort ascertained through routine clinical practice in one single hospital. In contrast, significant, but small differences of PRS burden in large-scale biobanks provide evidence that ICD-10 epilepsy codes are not the best substitutes for precise clinical classifications by experts, despite our efforts to identify patients with generalized or focal epilepsy using stringent ICD code filtering. In line with recent evidence, we observe that PRSs derived from a European cohort have lower power when applied to populations of different genetic architecture, as observed in the cohorts of Finnish and Japanese ancestry (Martin *et al.*, 2017).

By evaluating the PRS distribution, we identify patients with an effect size of polygenic variants at group level that is comparable to those in other studies with rare variants of large effect. Among the group of patients with high GE-PRS (top 0.5% of cases and controls with the highest scores), we observe an enrichment of patients with generalized epilepsy similar to that seen among carriers of established genetic risk factors, such as copy number variations and *de novo* variants: the largest copy number variation burden study in epilepsy to date showed a 7.45-fold enrichment of patients with generalized epilepsy (2.78% of all patients with generalized epilepsy) among all hotspot copy number variations carriers (cases/controls) (Pérez-Palma *et al.*, 2017). The largest *de novo* variant study in neurodevelopmental disorders with epilepsy showed a 4.6-fold excess of *de novo* variants in known genes associated with developmental and epileptic encephalopathies in neurodevelopmental disorders with epilepsy when compared to those without epilepsy (Heyne *et al.*, 2018). In this study, we identify a 4.63-fold enrichment of patients with generalized epilepsy in the top 0.5% highest GE-PRS in the Epi25 exploration cohort (2.39% of patients with generalized epilepsy) and a 4.47-fold enrichment of patients with generalized epilepsy in the top 0.5% highest GE-PRS in the clinical replication cohort (3.53% of patients with generalized epilepsy).

PRSs could have clinical implications for epilepsies because of their predictive power. Treatment with antiepileptic drugs after the first seizure has been debated, and the decision to start pharmacological treatment is usually based

on relative risks, benefits, and lifestyle factors. After the first seizure, ~50% of individuals go on to have a second seizure within 3–5 years, with most recurrences occurring within the first year (Kho *et al.*, 2006; Wiebe *et al.*, 2008). Several factors can increase the risk of seizure recurrence, including abnormal results on neurological examination, brain imaging, or EEG, a family history of epilepsy, or a personal history of remote symptomatic seizures (Wiebe *et al.*, 2008). Patients at high risk for recurrence have been shown to benefit from immediate antiepileptic drug treatment after a first seizure compared to no treatment or delayed treatment (Kim *et al.*, 2006). For an individual with new-onset epilepsy, it is also critical to differentiate between a focal versus generalized epilepsy to inform the selection of the first-line antiseizure drug (Perucca *et al.*, 1998; Goldenberg, 2010). Differential diagnosis is especially challenging for focal epilepsy patients with secondary generalization or for those not found to have a relevant lesion on magnetic resonance imaging scans. A PRS indicating that a person is carrying an excessive amount of common risk variants for epilepsy or for generalized versus focal epilepsy could provide useful information for clinicians in deciding when to begin, and what type of treatment should be provided.

Future research should determine if and how well PRS can improve existing prediction models when combined with other factors, including established genetic risk factors of individually larger effect. Although our study represents the first of its kind in epilepsy, it needs to be replicated in a prospective setting. The predictive power of the PRS is determined by the genetic homogeneity of the GWAS from which the PRS is generated and that of the cohort to which it is applied. For epilepsy, a strong Eurocentric bias in the only available large scale GWAS is impeding PRS prediction in non-European individuals. Possible approaches to improve the predictive power in the non-European population, such as including the target population in the training data (Márquez-Luna *et al.*, 2017), have been explored, but to realize the full potential of the PRS, greater population diversity must be prioritized in future GWAS studies (Martin *et al.*, 2019). It is possible that PRSs for focal epilepsies currently lack power because this group is genetically and phenotypically more heterogeneous than the group of generalized epilepsy (Speed *et al.*, 2014; International League Against Epilepsy Consortium on Complex Epilepsies, 2018). The clinical value of the PRS will also be limited by the low prevalence rates of epilepsy, leading to high negative predictive values, but low positive predictive values. To facilitate the implementation of PRS into clinical practice, additional research with larger, better-differentiated cohorts from different populations with well-characterized epilepsy phenotypes will be needed.

In summary, common polygenic variant burden for epilepsy can be measured and is differently distributed among patients with epilepsy and controls as well as between the two main epilepsy phenotypes (i.e. generalized and focal).

PRS for epilepsies can provide physicians with an estimate of an individual's overall genetic risk for epilepsy that could aid in early diagnosis and targeted treatment in the future. In addition, a combination of rare and common variants that may predispose an individual to develop epilepsy provides a chance for more informative prediction tools that may lead to a paradigm shift from current practice in rare disorder genetics (presence or absence of a Mendelian, high-risk variant) to a liability threshold model that assumes for each individual a continuous liability composed of rare and common genetic risk variants.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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