Supplementary material

Polygenic burden in focal and generalized epilepsies

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1. **Epi25 Consortium**
2. **Acknowledgments**
3. **Additional funding**
4. **Supplementary Methods**

4.1. Study cohorts
4.2. Cases
4.3. Controls
4.4. Biobank repositories
4.5. Data quality control and imputation
4.6. Detection of overlapping individuals across cohorts
4.7. Polygenic risk scoring SNP quality control
4.8. *P*-value thresholding

5. **Supplementary Figures**

5.1. Supplementary Figure 1: Principal component analysis of the European-ancestry study cohorts and 1000 Genomes Project samples
5.2. Supplementary Figure 2: Genome-wide polygenic risk for generalized epilepsy or focal epilepsy in the Finnish-ancestry population isolate
5.3. Supplementary Figure 3: Odds ratios for GE by GE-PRS deciles
5.4. Supplementary Figure 4: Odds ratios for FE by FE-PRS deciles

6. **Supplementary Tables**

6.1. Supplementary Table 1: GE- and FE-PRS in the European-ancestry exploration and replication cohorts
6.2. Supplementary Table 2: GE- and FE-PRS in the Finnish-ancestry population isolate
6.3. Supplementary Table 3: GE- and FE-PRS in the UKB, BioVU, and BBJ biobanks
6.4. Supplementary Table 4: *P*-value thresholding for GE-PRS
6.5. Supplementary Table 5: *P*-value thresholding for FE-PRS
6.6. Supplementary Table 6: Sample quality control filtering
6.7. Supplementary Table 7: Numbers of SNP considered for PRS
6.8. Supplementary Table 8: Diagnostic accuracy of the PRS in the *Epi25-EUR* and *Cleveland-EUR* cohorts

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4. Supplementary Methods

4.1. Study cohorts

Patients or their legal guardians provided signed informed consent according to local IRB requirements. Samples had been collected over 20 years in some centers, so the consent forms reflected standards at the time of collection. For Epi25 Consortium samples collected after January 25, 2015, consent forms required specific language according to the NIH Genomic Data Sharing Policy (https://osp.od.nih.gov/wp-content/uploads/NIH_GDS_Policy.pdf).

4.2. Cases

We used three independent patient cohorts, each consisting of individuals with generalized epilepsy (GE) or focal epilepsy (FE). The first cohort was derived from the European-ancestry subsample of the Epi25 project, an international multi-center epilepsy genetics research consortium, comprising 5,705 people with GE (*GE-Epi25-EUR* cohort) or FE (*FE-Epi25-EUR* cohort) after quality control (QC). The second cohort was derived from a single clinical center, the Cleveland Clinic Epilepsy Center, comprising 620 people with GE (*GE-Cleveland-EUR*) or FE (*FE-Cleveland-EUR*) after QC, all of European ancestry. The third cohort was derived from the Finnish-ancestry subsample of the Epi25 project that was not part of the first cohort, comprising 449 people with GE (*GE-Epi25-FIN*) or FE (*FE-Epi25-FIN*) after QC. All cohorts are detailed in Table 1. All three patient cohorts were genotyped with Illumina's Global Screening Array. GE and FE were diagnosed in all cohorts according to clinical criteria (clinical interview, neurological examination, EEG, imaging data). International League Against Epilepsy (ILAE) classifications (Berg *et al.*, 2010) were strictly followed in the Epi25 cohorts.

4.3. Controls

The European-ancestry epilepsy cohorts were matched to population controls from four merged cohorts: (1) healthy individuals from the Epi25 project (N = 210); (2) an in-house project on inflammatory bowel disease without reported epilepsy (N = 4,905); (3) healthy individuals from the Genetics of Personality Consortium (N = 463); and (4) population controls without reported epilepsy or potentially epileptogenic brain diseases (G40: epilepsy and recurrent seizures, C71: malignant neoplasm of brain, F44.5: conversion disorder with seizures or convulsions, G81.0:

flaccid hemiplegia, G93: other disorders of brain, I61: nontraumatic intracerebral hemorrhage,, I67: other cerebrovascular diseases, P90: convulsions of newborn, R56.0: febrile convulsions) from the Partners HealthCare Biobank (N = 14,875) (Karlson *et al.*, 2016). The first three control cohorts were genotyped with Illumina's Global Screening Array. The fourth control cohort was genotyped with Illumina's Multi-Ethnic Global Screening Array. The merged population cohort comprised 20,435 controls after QC. Population controls for the Finnish-ancestry cohort were obtained from the THL Institute for Health and Welfare (subsample of the FINRISK study, N = 1,559) (Borodulin *et al.*, 2017). The Finnish-ancestry cohort was genotyped on the Illumina's Global Screening Array.

4.4. Biobank repositories

Three large-scale biobank repositories were available as additional replication cohorts: UK Biobank (UKB), N = 383,656 (Sudlow *et al.*, 2015); Vanderbilt University biorepository (BioVU), N = 49,494 (Roden *et al.*, 2008); BioBank Japan (BBJ), N = 168,680 (Nagai *et al.*, 2017). Seizure or epilepsy classification was available as International Classification of Diseases (ICD-10) codes. We used ICD-10 G40.3 codes to identify people with GE, and G40.0 to G40.2 codes to identify people with FE. To increase the phenotypic homogeneity of each group, we excluded people with ICD-10 codes for both seizure types. In addition, we excluded subjects with epilepsy and other potentially epileptogenic brain diseases (ICD-10 C71: malignant neoplasm of brain, I61: nontraumatic intracerebral hemorrhage, I67: other cerebrovascular diseases, G81: hemiplegia and hemiparesis, G93: other disorders of brain, Q28: other congenital malformations of circulatory system).

4.5. Data quality control and imputation

Before imputation, we excluded genotyped individuals based on the following criteria: (1) genotype call rate < 0.95; (2) high (> 0.2) or low (< -0.2) inbreeding coefficient estimate of the observed versus expected number of homozygous genotypes; (3) missing, ambiguous, or sex mismatch between X-chromosome genotype and reported gender; (4) population outliers not clustering with the 1000 Genomes Project (1000 Genomes Project Consortium *et al.*, 2015) European samples in a principal component analysis (Supplementary Fig. 1). Then, we excluded single-nucleotide polymorphisms (SNPs) based on the following criteria: (1) SNP call rate < 0.98 in the combined case/control dataset; (2) minor allele frequency (MAF) < 0.01; (3) deviation from the Hardy-Weinberg equilibrium with $P < 1 \times 10^{-6}$. Sample and SNP QC

procedures were performed using PLINK v1.9 (Chang *et al.*, 2015) and GCTA (Yang *et al.*, 2011). The genotyped dataset was aligned to the imputation reference (variant name, variant position, and strand orientation) using the Genotype Harmonizer (Deelen *et al.*, 2014). Imputation to the Haplotype Reference Consortium (HRC) reference r1.1 (McCarthy *et al.*, 2016) was performed using reference-based phasing with Eagle v2.4 (Loh *et al.*, 2016) and Minimac4 (https://github.com/statgen/Minimac4), as implemented on the Michigan Imputation Server (Das *et al.*, 2016). After imputation, we removed randomly one individual from each pair of individuals with 3rd-degree relationships and higher (kinship coefficient > 0.0442) using KING (Manichaikul *et al.*, 2010). Detailed information on all excluded individuals is given in Supplementary Table 6.

4.6. Detection of overlapping individuals across cohorts

A proportion of cases and controls who were part of the prior GWAS (International League Against Epilepsy Consortium on Complex Epilepsies, 2018) and thus contributed to PRS development, were also genotyped in our study cohorts. These individuals were excluded from the study cohorts. Inspired by the one-way cryptographic hash function (Turchin and Hirschhorn, 2012), we used a protocol that allows overlapping participants between studies to be identified without sharing individual-level data. One-way cryptographic hashes are a form of security algorithms that alter input data in such a way that the resulting output data cannot be reverted feasibly to the original form. To identify overlapping individuals, we first generated ten batches of SNPs, which did not have missing genotypes in any individual in this study or the GWAS used as the source for the generation of the PRS (N_{SNP} = 25). We then computed hash values (checksums) for each of the ten batches for each individual, using the "cksum" command, which is routinely available in Linux operating systems. The "cksum" command will always generate the same unique hash value for each batch, when using the same SNPs, with the same information (same non-missing genotype), and in the same order (sorted by physical position). We then marked every pair of individuals with one or more identical hash values (out of the ten) as duplicate and excluded the corresponding individual from our study. The procedure is implemented in perl and freely available at https://personal.broadinstitute.org/sripke/share_links/checksums_download/.

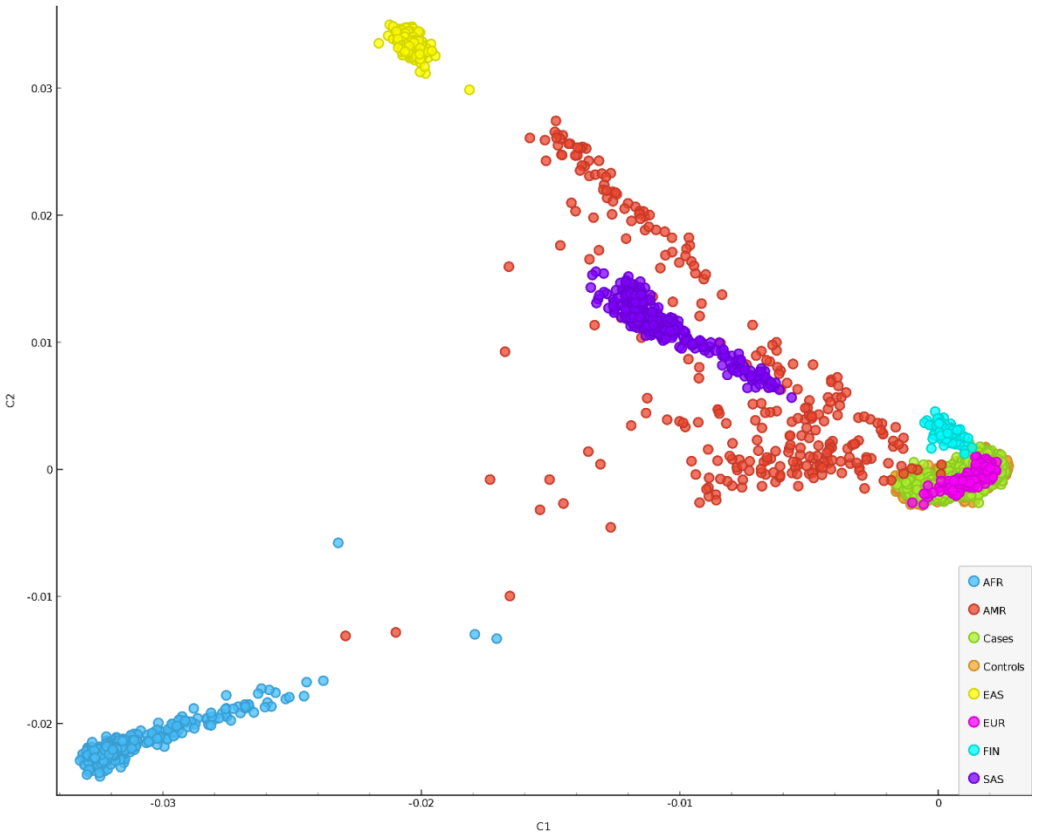
4.7. Polygenic risk scoring SNP quality control

We selected high-quality imputed and genotyped SNPs in the study cohorts based on the following criteria and established best practices (Choi *et al.*, 2018): (1) Minimac4 imputation quality score, $R^2 > 0.3$; (2) Minimac4 squared correlation value between masked genotypes of genotyped SNPs and the imputed dosages, Emp-$R^2 > 0.3$; (3) call rate > 0.98 in either cases or controls; (4) minor allele frequency > 2% in either cases or controls; (5) deviation from the Hardy-Weinberg equilibrium with $P > 10^{-7}$ in either cases or controls; (6) SNPs with non-ambiguous alleles (A/T or C/G excluded). We generated PRS based on the overlap of the remaining SNPs and GWAS SNPs with available summary statistics, pruned to a subset of uncorrelated SNPs ($r^2 < 0.1$ within 500kb from the most significant SNP in each locus). The numbers of SNPs available for PRS generation are detailed in Supplementary Table 7.

4.8. *P*-value thresholding

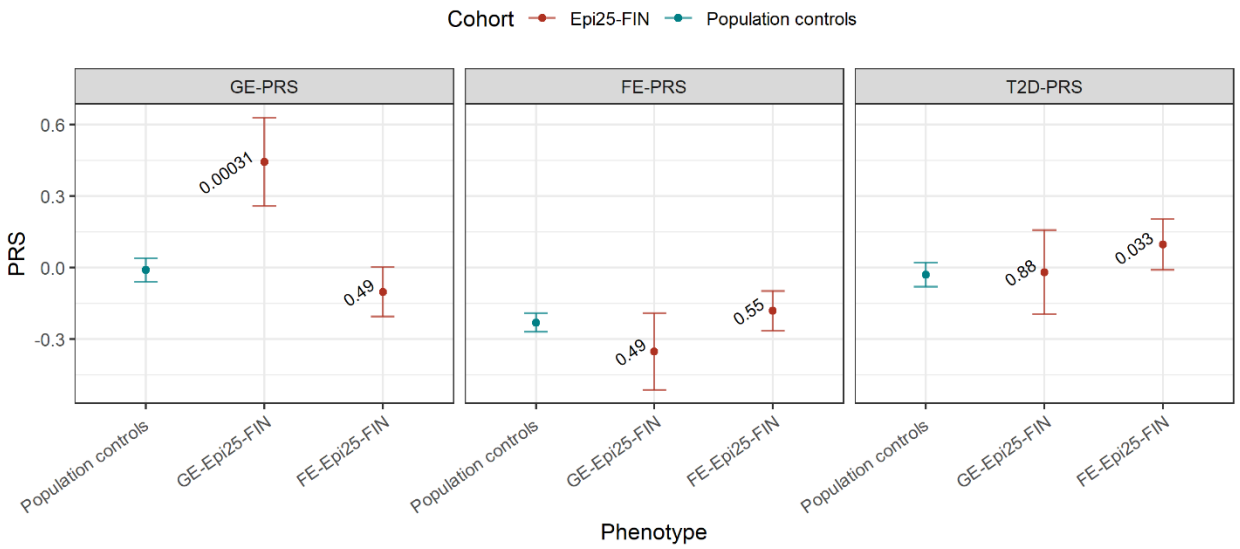
To identify the optimal *P*-value threshold for PRS prediction, we performed a random split of our exploration cohort (Epi25-EUR, 5,705 European-ancestry individuals: 80% training, 20% validation), and generated GE-PRS (Supplementary Table 4) and FE-PRS (Supplementary Table 5) at eight *P*-value thresholds (PT = 10^{-4}, 10^{-3}, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5) in the corresponding training samples. The performance of the best predicting threshold was explored in the validation samples. GE-PRS predicted the GE vs. control status best at PT=0.5 in the training sample. The threshold was confirmed in the validation sample by a significant prediction and a similar level of the explained phenotypic variance (training: 2.79% / validation: 2.86%). FE-PRS predicted the FE vs. control status best at PT=0.1. In the validation sample we observed a slight loss of power at PT=0.1, when considering the explained phenotypic variance (training: 0.62% / validation: 0.28%). For a homogeneous methodology for the whole study, we also explored PT=0.5 in the FE validation sample and observed a more significant prediction and a full recovery of the explained phenotypic variance (training: 0.56% / validation: 0.52%). Subsequently, PT=0.5 was considered as the optimal PT for FE, because of negligible differences of the prediction power at all PTs from 0.1 to 0.5 in the training sample. The identified optimal *P*-value threshold (0.5 for GE and FE) was applied for all datasets.

5. Supplementary Figures



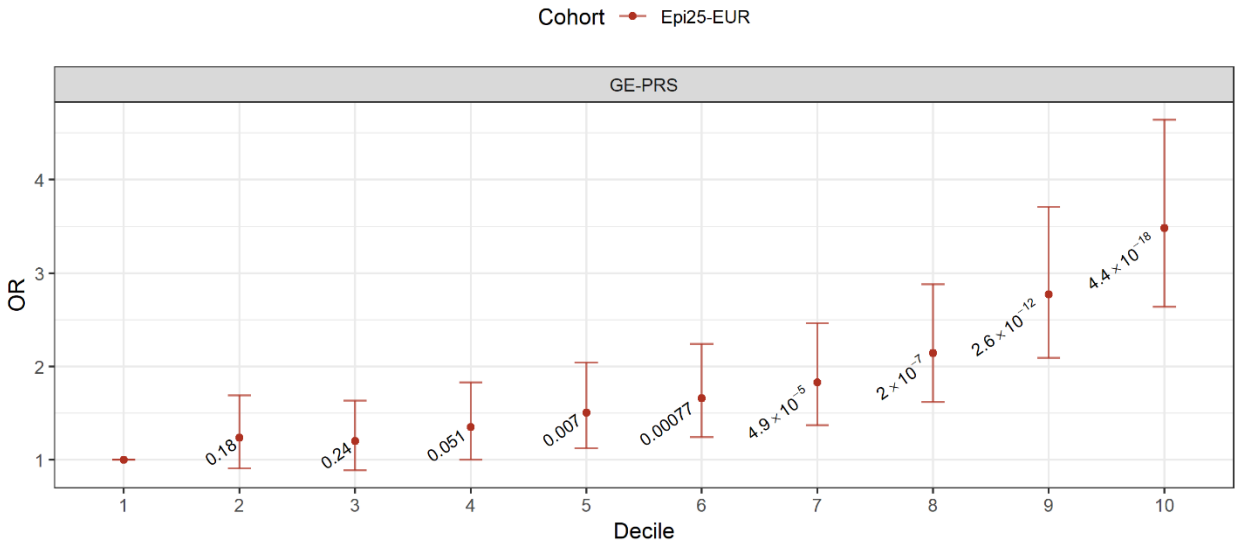
Supplementary Figure 1: Principal component analysis of the European-ancestry study cohorts and 1000 Genomes Project samples

Legend: C1: PCA principal component 1, C2: PCA principal component 2, AFR: 1000 Genomes African samples, AMR: 1000 Genomes admixed American samples, Cases: European Epi25 Consortium and Cleveland Clinic samples, Controls: European merged population samples, EAS: 1000 Genomes East Asian samples, EUR: 1000 Genomes European samples, FIN: 1000 Genomes South Finnish samples, SAS: 1000 Genomes South Asian samples.



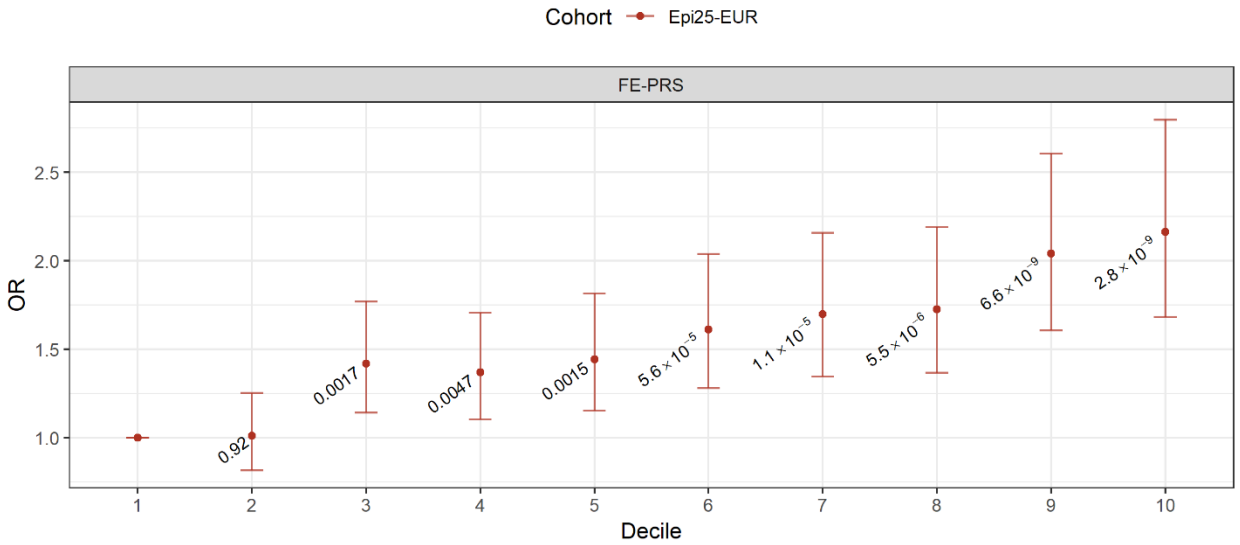
Supplementary Figure 2: Genome-wide polygenic risk for generalized epilepsy or focal epilepsy in the Finnish-ancestry population isolate

Shown are the means of the standardized GE-, FE-, and T2D-PRS with 95% confidence intervals for the Finnish-ancestry population controls (highlighted in blue; N = 1,559) and the Finnish-ancestry generalized epilepsy and focal epilepsy Epi25 cohorts (highlighted in red; *GE-Epi25-FIN* N = 112; *FE-Epi25-FIN* N = 337). 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).



Supplementary Figure 3: Odds ratios for GE by GE-PRS deciles

Based on the GE-PRS, individuals with GE and controls were allocated to 10 deciles containing near identical numbers of individuals. Decile 1 contained the lowest scores and was used as reference for deciles 2-10 that had increasingly higher GE-PRS. Odds ratios and *P*-values were calculated using a logistic regression model of deciles 2-10 against decile 1, adjusted for sex and the first four principal components of ancestry. The points represent the odds ratios. The bars represent the lower and upper confidence intervals of the odds ratios.



Supplementary Figure 4: Odds ratios for FE by FE-PRS deciles

Based on the FE-PRS, individuals with FE and controls were allocated to 10 deciles containing near identical numbers of individuals. Decile 1 contained the lowest scores and was used as reference for deciles 2-10 that had increasingly higher FE-PRS. Odds ratios and *P*-values were calculated using a logistic regression model of deciles 2-10 against decile 1, adjusted for sex and the first four principal components of ancestry. The points represent the odds ratios. The bars represent the lower and upper confidence intervals of the odds ratios.

6. Supplementary Tables

Supplementary Table 1: GE- and FE-PRS in the European-ancestry exploration and replication cohorts

					GE-PRS (N_{SNP} = 50,515)		FE-PRS (N_{SNP} = 51,333)		T2D-PRS (N_{SNP} = 72,305)	
Center/Study	**Ethnicity**	**Epilepsy**	**Cases, N**	**Controls, N**	***P*-value**	**% R^2**	***P*-value**	**% R^2**	***P*-value**	**% R^2**
Epi25-EUR	EUR	GE	2,256	20,435	2.35E-70	2.83	1.71E-15	0.56	0.61	0.002
Cleveland-EUR	EUR	GE	85	20,435	1.43E-07	2.58	4.72E-03	0.74	0.92	0.001
Epi25-EUR	EUR	FE	3,449	20,435	8.21E-18	0.51	5.74E-19	0.55	8.48E-03	0.05
Cleveland-EUR	EUR	FE	535	20,435	6.12E-04	0.26	1.69E-06	0.51	0.017	0.13
Epi25-EUR	EUR	GE vs. FE	2,256	3,449	1.64E-15	1.74	0.84	0.001	0.40	0.02
Cleveland-EUR	EUR	GE vs. FE	85	535	2.85E-04	3.87	0.42	0.19	0.30	0.31

P-values were calculated using 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). Legend: PRS: polygenic risk score, N: number, SNP: single nucleotide polymorphism, GE: generalized epilepsy, FE: focal epilepsy, T2D: Type 2 diabetes, EUR: European, % R^2: percentage of explained variance (Nagelkerke's pseudo-R^2).

Supplementary Table 2: GE- and FE-PRS in the Finnish-ancestry population isolate

					GE-PRS (N_{SNP} = 59,006)		FE-PRS (N_{SNP} = 59,728)		T2D-PRS (N_{SNP} = 110,915)	
Center/Study	**Ethnicity**	**Epilepsy**	**Cases, N**	**Controls, N**	***P*-value**	**% R^2**	***P*-value**	**% R^2**	***P*-value**	**% R^2**
Epi25-FIN	FIN	GE	112	1559	3.11E-04	2.01	0.49	0.04	0.88	0.003
Epi25-FIN	FIN	FE	337	1559	0.49	0.04	0.55	0.03	0.033	0.39
Epi25-FIN	FIN	GE vs. FE	112	337	1.80E-04	4.58	0.35	0.27	0.36	0.26

P-values were calculated using 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). Legend: PRS: polygenic risk score, N: number, SNP: single nucleotide polymorphism, GE: generalized epilepsy, FE: focal epilepsy, T2D: Type 2 diabetes, FIN: Finnish, % R^2: percentage of explained variance (Nagelkerke's pseudo-R^2).

Supplementary Table 3: GE- and FE-PRS in the UKB, BioVU, and BBJ biobanks

UK Biobank					**GE-PRS (N_{SNP} = 62,986)**		**FE-PRS (N_{SNP} = 63,730)**		**T2D-PRS (N_{SNP} = 143,464)**	
Center/Study	**Ethnicity**	**Epilepsy**	**Cases, N**	**Controls, N**	***P*-value**	**% R^2**	***P*-value**	**% R^2**	***P*-value**	**% R^2**
UKB	EUR	GE	246	383,197	2.89E-02	0.12	0.069	0.08	0.88	0.001
UKB	EUR	FE	213	383,197	0.063	0.10	0.44	0.02	0.84	0.001
Vanderbilt biorepository					**GE-PRS (N_{SNP} = 87,758)**		**FE-PRS (N_{SNP} = 88,468)**		**T2D-PRS (N_{SNP} = 246,721)**	
Center/Study	**Ethnicity**	**Epilepsy**	**Cases, N**	**Controls, N**	***P*-value**	**% R^2**	***P*-value**	**% R^2**	***P*-value**	**% R^2**
BioVU	EUR	GE	293	48,665	1.09E-02	0.19	0.88	0.001	0.85	0.001
BioVU	EUR	FE	536	48,665	0.37	0.01	0.23	0.03	0.61	0.005
BioBank Japan					**GE-PRS (N_{SNP} = 52,021)**		**FE-PRS (N_{SNP} = 52,504)**		**T2D-PRS (N_{SNP} = 65,379)**	
Center/Study	**Ethnicity**	**Epilepsy**	**Cases, N**	**Controls, N**	***P*-value**	**% R^2**	***P*-value**	**% R^2**	***P*-value**	**% R^2**
BBJ	JPN	GE	219	168,356	0.33	0.03	0.32	0.03	0.45	0.02
BBJ	JPN	FE	105	168,356	0.55	0.02	0.29	0.06	0.096	0.16

P-values were calculated using 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 $\alpha = 1.67 \times 10^{-2}$ (two tests per cohort and one meta-analysis). Legend: PRS: polygenic risk score, UKB: UK Biobank, BioVU: Vanderbilt University biorepository, BBJ: BioBank Japan, N: number, SNP: single nucleotide polymorphism, GE: generalized epilepsy, FE: focal epilepsy, T2D: Type 2 diabetes, EUR: European, JPN: Japanese, % R^2: percentage of explained variance (Nagelkerke's pseudo-R^2).

Supplementary Table 4: *P*-value thresholding for GE-PRS

Training set	**Ethnicity**	**Epilepsy**	**Cases, N**	**Controls, N**	***P*-value threshold**	***P*-value**	**% R^2**	**N_{SNP}**
Epi25-EUR (80% samples)	EUR	GE	1,805	16,348	0.0001	5.89E-20	0.93	165
Epi25-EUR (80% samples)	EUR	GE	1,805	16,348	0.001	1.32E-36	1.78	772
Epi25-EUR (80% samples)	EUR	GE	1,805	16,348	0.05	1.57E-52	2.61	11,562
Epi25-EUR (80% samples)	EUR	GE	1,805	16,348	0.1	4.83E-55	2.74	19,032
Epi25-EUR (80% samples)	EUR	GE	1,805	16,348	0.2	6.22E-55	2.74	29,620
Epi25-EUR (80% samples)	EUR	GE	1,805	16,348	0.3	4.10E-54	2.70	38,005
Epi25-EUR (80% samples)	EUR	GE	1,805	16,348	0.4	4.24E-55	2.75	44,794
Epi25-EUR (80% samples)	EUR	GE	1,805	16,348	0.5	8.30E-56	2.79	50,530
Validation set	Ethnicity	Epilepsy	Cases, N	Controls, N	*P*-value threshold	*P*-value	% R^2	N_{SNP}
Epi25-EUR (20% samples)	EUR	GE	451	4,087	0.5	1.32E-15	2.86	50,482

Eight *P*-value thresholds (10^{-4}, 10^{-3}, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5) were tested in a random split of the GE exploration cohort (*GE-Epi25-EUR*) into training (80%) and validation (20%). The optimal *P*-value threshold is highlighted with a blue border. Legend: N: number, % R^2: percentage of explained variance (Nagelkerke's pseudo-R^2), SNP: single nucleotide polymorphism, GE: generalized epilepsy.

Supplementary Table 5: *P*-value thresholding for FE-PRS

Training set	Ethnicity	Epilepsy	Cases, N	Controls, N	*P*-value threshold	*P*-value	% R^2	N_{SNP}
Epi25-EUR (80% samples)	EUR	FE	2,760	16,348	0.0001	0.78	6.52E-04	117
Epi25-EUR (80% samples)	EUR	FE	2,760	16,348	0.001	1.01E-03	0.09	694
Epi25-EUR (80% samples)	EUR	FE	2,760	16,348	0.05	1.33E-13	0.48	11,721
Epi25-EUR (80% samples)	EUR	FE	2,760	16,348	0.1	3.74E-17	0.62	19,394
Epi25-EUR (80% samples)	EUR	FE	2,760	16,348	0.2	1.88E-15	0.55	30,071
Epi25-EUR (80% samples)	EUR	FE	2,760	16,348	0.3	2.94E-16	0.58	38,499
Epi25-EUR (80% samples)	EUR	FE	2,760	16,348	0.4	1.12E-15	0.56	45,571
Epi25-EUR (80% samples)	EUR	FE	2,760	16,348	0.5	7.80E-16	0.56	51,336
Validation set	**Ethnicity**	**Epilepsy**	**Cases, N**	**Controls, N**	***P*-value threshold**	***P*-value**	**% R^2**	**N_{SNP}**
Epi25-EUR (20% samples)	EUR	FE	689	4,087	0.1	4.36E-03	0.28	19,393
Epi25-EUR (20% samples)	EUR	FE	689	4,087	0.5	1.10E-04	0.52	51,321

Eight *P*-value thresholds (10^{-4}, 10^{-3}, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5) were tested in a random split of the FE exploration cohort (*FE-Epi25-EUR*) into training (80%) and validation (20%). The optimal *P*-value thresholds are highlighted with blue borders. Legend: N: number, % R^2: percentage of explained variance (Nagelkerke's pseudo-R^2), SNP: single nucleotide polymorphism, FE: focal epilepsy.

Supplementary Table 6: Sample quality control filtering

Cohort	Epi25		Cleveland		
Phenotype	**GE**	**FE**	**GE**	**FE**	**Controls**
Available samples before quality control	4,613	6,809	97	633	28,187
Low genotyping call rate < 0.95	-18	-11	0	0	-8
High (> 0.2) or low (< -0.2) inbreeding coefficient estimate	-21	-46	0	0	-67
Missing sex	-10	-7	0	-1	-37
Ambiguous sex (undeterminable by genotypes)	-10	-43	0	0	-3
Mismatch between genotyped and reported gender	-102	-99	0	0	-154
Non-European individuals	-791	-752	-11	-92	-5026
Imputation	3,661	5,851	86	540	22,892
Related individuals across study cohorts	-114	-115	0	-1	-809
Overlapping individuals across study cohorts and GWAS	-1179	-1950	-1	-4	-89
Samples available for PRS after quality control	2,368	3,786	85	535	21,994

Overview of the Epi25 (EUR and FIN) and Cleveland Clinic cohorts before and after quality control filtering for PRS generation.

Supplementary Table 7: Numbers of SNP considered for PRS

	N	
Imputed SNPs before QC	30,260,497	
SNPs after post-imputation QC (Supplementary material 4.7)	2,194,578	
SNPs for PRS after P-value thresholding and LD-pruning (Supplementary material 4.7 and 4.8)	N	mean absolute Beta
GE-PRS in EUR samples	50,515	0.0073
FE-PRS in EUR samples	51,333	0.0090
T2D-PRS in EUR samples	72,305	0.0012
GE-PRS in FIN samples	59,006	0.0074
FE-PRS in FIN samples	59,728	0.0093
T2D-PRS in FIN samples	110,915	0.0017

Supplementary Table 8: Diagnostic accuracy of the PRS in the *Epi25-EUR* and *Cleveland-EUR* cohorts

GE-PRS / *GE-Epi25*	**cases/controls upper PRS%**	**cases/controls lower PRS%**	**Sensitivity**	**Specificity**	**PPV (0.433% prevalence)**	**NPV (0.433% prevalence)**
Top 20% of distribution	887/3,652	1,369/16,783	0.393	0.821	0.009	0.997
Top 5% of distribution	305/830	1,951/19,605	0.135	0.959	0.014	0.996
Top 0.5% of distribution	54/60	2,202/20,375	0.024	0.997	0.034	0.996
GE-PRS / *GE-Cleveland*	**cases/controls upper PRS%**	**cases/controls lower PRS%**	**Sensitivity**	**Specificity**	**PPV (0.433% prevalence)**	**NPV (0.433% prevalence)**
Top 20% of distribution	35/4,070	50/16,365	0.412	0.801	0.009	0.997
Top 5% of distribution	11/1,016	74/19,419	0.129	0.950	0.011	0.996
Top 0.5% of distribution	3/100	82/20,335	0.035	0.995	0.030	0.996
FE-PRS / *FE-Epi25*	**cases/controls upper PRS%**	**cases/controls lower PRS%**	**Sensitivity**	**Specificity**	**PPV (0.299% prevalence)**	**NPV (0.299% prevalence)**
Top 20% of distribution	992/3,785	2,457/16,650	0.288	0.815	0.005	0.997
Top 5% of distribution	292/903	3,157/19,532	0.085	0.956	0.006	0.997
Top 0.5% of distribution	40/80	3,409/20,355	0.012	0.996	0.009	0.997
FE-PRS / *FE-Cleveland*	**cases/controls upper PRS%**	**cases/controls lower PRS%**	**Sensitivity**	**Specificity**	**PPV (0.299% prevalence)**	**NPV (0.299% prevalence)**
Top 20% of distribution	148/4,047	387/16,388	0.277	0.802	0.004	0.997
Top 5% of distribution	40/1,009	495/19,426	0.075	0.951	0.005	0.997
Top 0.5% of distribution	5/100	530/20,335	0.009	0.995	0.006	0.997

The positive predictive values (PPV) and negative predictive values (NPV) are calculated based on pooled point prevalence of 4.33/1000 for active generalized epilepsy, 2.99/1000 for focal epilepsy (Fiest *et al.*, 2017).

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