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Negative results

Analysis of shared common genetic risk between amyotrophic lateral sclerosis and epilepsy

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ABSTRACT

Because hyper-excitability has been shown to be a shared pathophysiological mechanism, we used the latest and largest genome-wide studies in amyotrophic lateral sclerosis ($n = 36,052$) and epilepsy ($n = 38,349$) to determine genetic overlap between these conditions. First, we showed no significant genetic correlation, also when binned on minor allele frequency. Second, we confirmed the absence of polygenic overlap using genomic risk score analysis. Finally, we did not identify pleiotropic variants in meta-analyses of the 2 diseases. Our findings indicate that amyotrophic lateral sclerosis and epilepsy do not share common genetic risk, showing that hyper-excitability in both disorders has distinct origins.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by the progressive degeneration of motor neurons. Cramps and fasciculations are common in ALS patients and indicate axonal hyper-excitability in motor neurons (Kanai et al., 2006). Proposed mechanisms for hyper-excitability in ALS include impaired inhibitory signaling through GABAergic interneurons, astrocytes failing to adequately regulate glutamate levels and extracellular K+ concentrations at the synaptic cleft, and altered ion channel expression in motor neurons (Do-Ha et al., 2018). Ion channel dysfunction has been correlated to muscle weakness and motor neuron degeneration (Geevasinga et al., 2015), while peripheral hyper-excitability and central hyper-excitability are furthermore strong predictors of shorter survival (Kanai et al., 2012; Shimizu et al., 2018). Similarly, in epilepsy, an imbalance of excitatory and inhibitory mechanisms in the brain contributes to seizure pathogenesis. Interestingly, the anti-epileptic drug retigabine has shown acute beneficial effects on peripheral nerve excitability in ALS (Kovalchuk et al., 2018). Of further note, riluzole—a drug used in the treatment of ALS—has been shown to decrease hippocampal epileptiform activity and reduce seizure activity in epilepsy animal models (Diao et al., 2013; Kim et al., 2007).

The beforementioned observations and the availability of recent and large genome-wide association study (GWAS) datasets (The International League Against Epilepsy Consortium on Complex Epilepsies, 2018; van Rheenen et al., 2016), showing that the heritability of each of the 2 diseases is partly explained by common genetic variation, have led us to investigate whether ALS and epilepsy share any common genetic risk.

A list of consortium members (Project MinE ALS GWAS Consortium and the International League Against Epilepsy Consortium on Complex Epilepsies) is provided in the Supplementary Material.

A full reference list is provided in the Supplementary Material.

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2. Methods

We used individual level data of subjects with European ancestry from recent large GWASs in ALS (N = 12,577 cases; 23,475 controls) (van Rheenen et al., 2016) and epilepsy (N = 14,131 cases; 24,218 controls), including sets of focal (n = 9095 cases) and generalized (n = 3305 cases) epilepsy subtypes (The International League Against Epilepsy Consortium on Complex Epilepsies, 2018). We then performed genetic correlation analyses, genomic risk score (GRS) analyses, and meta-analyses (Supplementary Methods).

3. Core data

We found no significant genetic correlations between ALS and epilepsy, including focal and generalized subtypes (Fig. 1). Furthermore, genetic risk for epilepsy was not associated with case–control status in the ALS dataset (Fig. 2A, Supplementary Table 3A), and similarly ALS GRSs did not associate with epilepsy status (Fig. 2B, Supplementary Table 3B). Inverse-variance weighted meta-analyses of ALS and epilepsy revealed several loci passing the threshold for genome-wide significance (Fig. 3, Supplementary Figs. 2 and 3, Supplementary Table 4). Only the locus near *BMP8A* in the ALS-epilepsy (all subtypes combined) analysis (Fig. 3A) fulfilled criteria for a pleiotropic locus with nominal-significant association p-values ($p < 0.05$) in both studies independently (ALS, $p = 2.3 \times 10^{-2}$; epilepsy, $p = 8.7 \times 10^{-8}$) and a genome-wide significant p-value in meta-analysis ($p = 3.2 \times 10^{-8}$, odds ratio = 1.02, similar effect directions). This variant, however, was not associated with ALS ($p = 0.11$) in a larger GWAS for which only summary statistics were available (Nicolas et al., 2018).

4. Discussion

We have used the latest and largest individual-level genotype datasets for ALS and epilepsy to perform the most comprehensive cross-disorder genome-wide study between these diseases available to date. This has enabled careful control of sample overlap and relatedness between datasets. Also, many tools for cross-disorder analyses have increased power because they use individual-level genotype data instead of summary statistics. Moreover, the genetic correlation estimate between these disorders was not reported in a recent large-scale study on shared polygenic risk in ALS (Bandres Ciga et al., 2019). Overall, we showed with the currently available sample sizes that ALS and epilepsy are not genetically correlated, and that GRS capturing combined effects of common variants in one disease do not explain phenotypic variance in the other disease and that no loci with an effect in both ALS and epilepsy were identified in meta-analyses.

The loci near *BMP8A* and *PTPRK* initially showed evidence for pleiotropy, because of their nominal significant association in both ALS and epilepsy GWAS and stronger statistical association in the meta-analysis and sign-independent meta-analysis, respectively. Nevertheless, the associations of top single-nucleotide polymorphisms (SNPs) in these loci with ALS were weak and did not reach nominal significance in a more recent and larger ALS GWAS meta-analysis (Nicolas et al., 2018), which combined logistic regression association results from summary-level data of van Rheenen et al. (2016) and individual-level data of additional cohorts. Although the meta-analysis framework applied in that larger study could be less powerful compared to a mixed linear model approach with full individual-level data, we were unable prove pleiotropy for these loci. Since only summary statistics of that larger ALS GWAS meta-analysis were available, we were furthermore unable to perform all our analyses including those data. Moreover, the contribution of epilepsy to the pleiotropic signals was large with association p-values around the genome-wide significance threshold (The International League Against Epilepsy Consortium on Complex Epilepsies, 2018). These results do not support the notion that these loci are associated with both diseases.

Our results find support in epidemiological data reporting an absence of comorbidity between ALS and epilepsy (Tartaglia et al., 2007), although case reports of co-occurrence in *C9orf72* repeat expansion carriers exist (Capasso et al., 2016; Janssen et al., 2016; van den Ameele et al., 2018). Detailed *C9orf72* repeat expansion status was currently unavailable in our ALS dataset. Although several sodium and potassium channel genes have been associated with epilepsy, and involvement of these channels in the development of cramps in ALS has been proposed (Helbig et al., 2008; Kanai et al., 2006; The International League Against Epilepsy Consortium on Complex Epilepsies, 2018), our results suggest that these clinical observations are not a consequence of shared polygenic architecture. Cramps in ALS might thus be a consequence of disease-specific pathology leading to a hyper-excitable state of motor neurons, for which anti-epileptic drugs can still be effective (Kovalchuk et al., 2018).

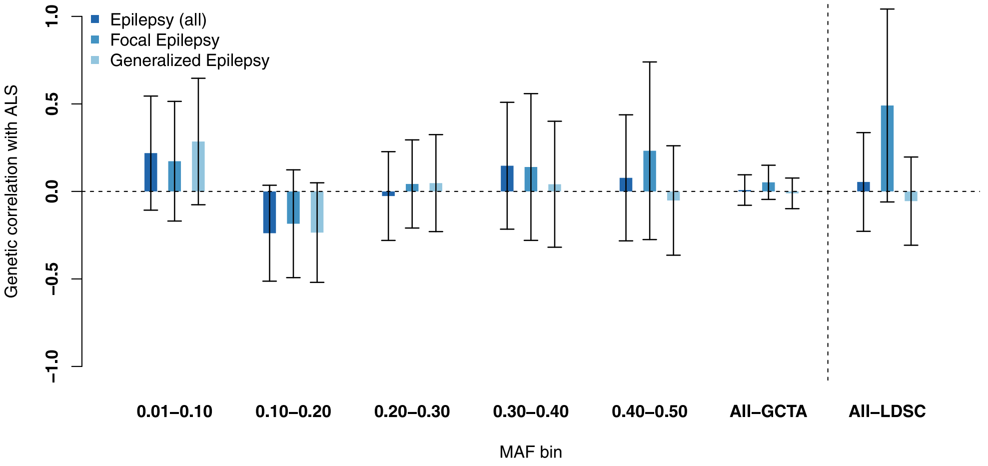

Fig. 1. Genetic correlation between ALS and epilepsy. Genetic correlation between ALS and epilepsy (including focal and generalized subtypes) (y-axis) was estimated based on all SNPs in the MAF range 0.01–0.5 (GCTA-All) and on SNPs in 5 MAF bins and using GCTA-GREML (x-axis). Furthermore, LDSC was used to estimate genetic correlation (All-LDSC). Error bars indicate 95% confidence intervals. Abbreviations: ALS, amyotrophic lateral sclerosis; GCTA, Genome-wide Complex Trait Analysis; GREML, genetic restricted maximum likelihood; LD, linkage disequilibrium; LDSC, linkage disequilibrium score regression; MAF, minor allele frequency; SNP, single-nucleotide polymorphism.

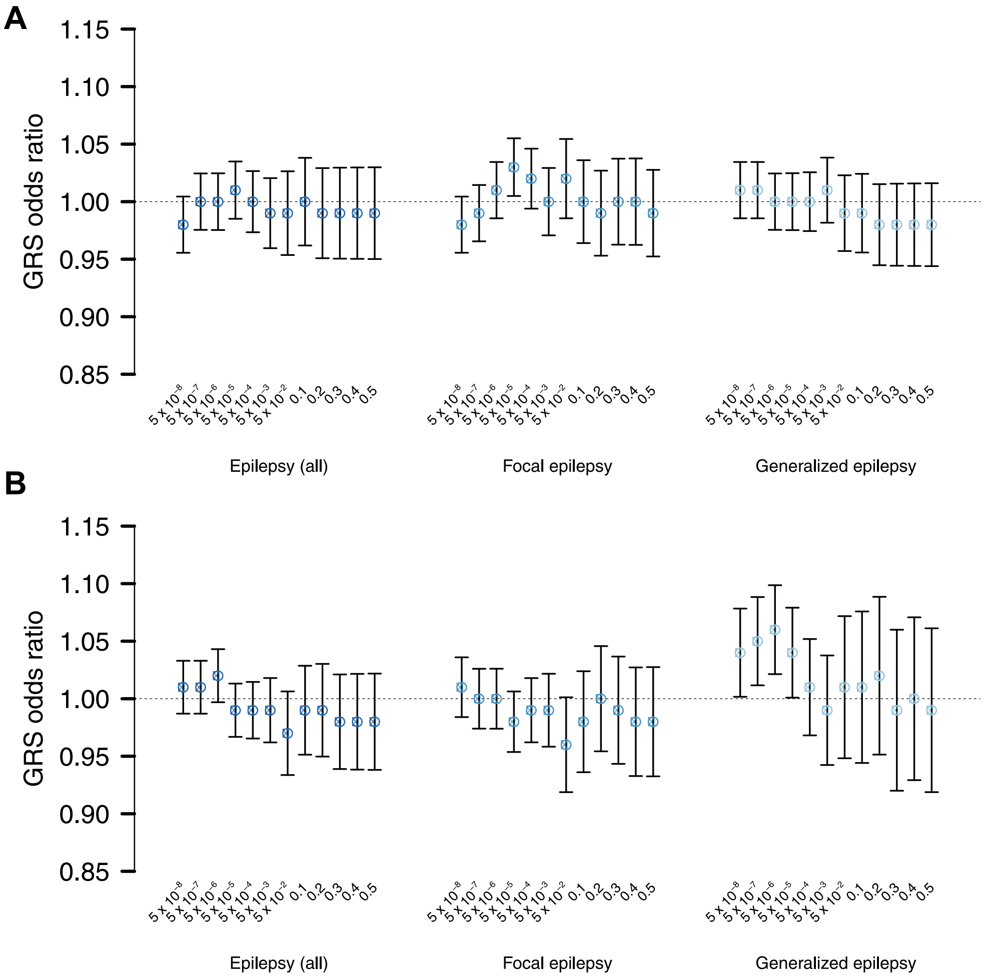

Fig. 2. GRS analysis results. Twelve GRSs were calculated per individual in the target dataset and tested for association with the target disease using logistic regression (*x*-axis). (A) Epilepsy GWAS results were used as discovery datasets, and ALS was used as the target dataset. (B) ALS GWAS results were used as the discovery dataset, and epilepsy and subtypes were used as target datasets. Odds ratios reflect the amount by which the odds of ALS (in A) or epilepsy (in B) changes per SD increase in GRS (all GRS were scaled around mean 0 with SD 1). Error bars indicate 95% confidence intervals. The *p*-value threshold for significant GRS association was Bonferroni-corrected for 6 analyses times 12 P_T ($p < 6.94 \times 10^{-4}$). Detailed results are shown in Supplementary Table 3. Abbreviations: ALS, amyotrophic lateral sclerosis; GRS, genomic risk score; GWAS, genome-wide association study; SD, standard deviation.

We have considered possible limitations of our study. First, we cannot rule out that a study with even larger datasets may possibly yield significant results. However, such a correlation would then be expected to be very small, as we have shown no sign of substantial shared genetic risk with the current large GWAS datasets we have analyzed. The current sample size provides 80% power to detect a genetic correlation of 0.091 at $\alpha = 0.05$ using GCTA-REML (Visscher et al., 2014). Second, rare genetic variation plays a role in both diseases. Although we found non-significant genetic correlation estimates in the lower minor allele frequency (MAF) spectrum of our data, variants with MAF < 0.01 cannot be reliably included in these GWAS analyses. Future GWAS studies employing rare-variant imputation or large-scale sequencing efforts may potentially provide more insight into shared heritability in the rare variant spectrum. Third, phenotypic heterogeneity in ALS and epilepsy might result in a dilution of signal of possible shared genetic underpinnings. Although we have tested genetic correlations with epilepsy subtypes (focal and generalized), a detailed characterization of both ALS and epilepsy patients could identify subgroups that share phenotypic and pathological characteristics that might share a genetic basis. However, at present such phenotypic information is unavailable at sufficiently large sample sizes for cross-disorder analyses.

Disclosure statement

This study was supported by a Marie-Curie Individual Fellowship (number 751761) from the European Commission, and NIH grant P01-AG-032953. This project has furthermore received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement no 772376 – EScORIAL). This is in part an EU Joint Program - Neurodegenerative Disease Research (JPND) project. The project is also supported through the following funding organizations under the aegis of JPND (www.jpnd.eu): United Kingdom, Medical Research Council (MR/L501529/1, MR/R024804/1); the Netherlands, ZONMW (grant no. 733051071); and through the Motor Neurone Disease Association. This study represents independent research part funded by the National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre. Samples used in this research were in part obtained from the UK National DNA Bank for MND Research, funded by the MND Association and the Wellcome Trust. We would like to thank people with MND and their families for their participation in this project.

Some of the data reported in this paper were collected as part of a project undertaken by the International League against Epilepsy

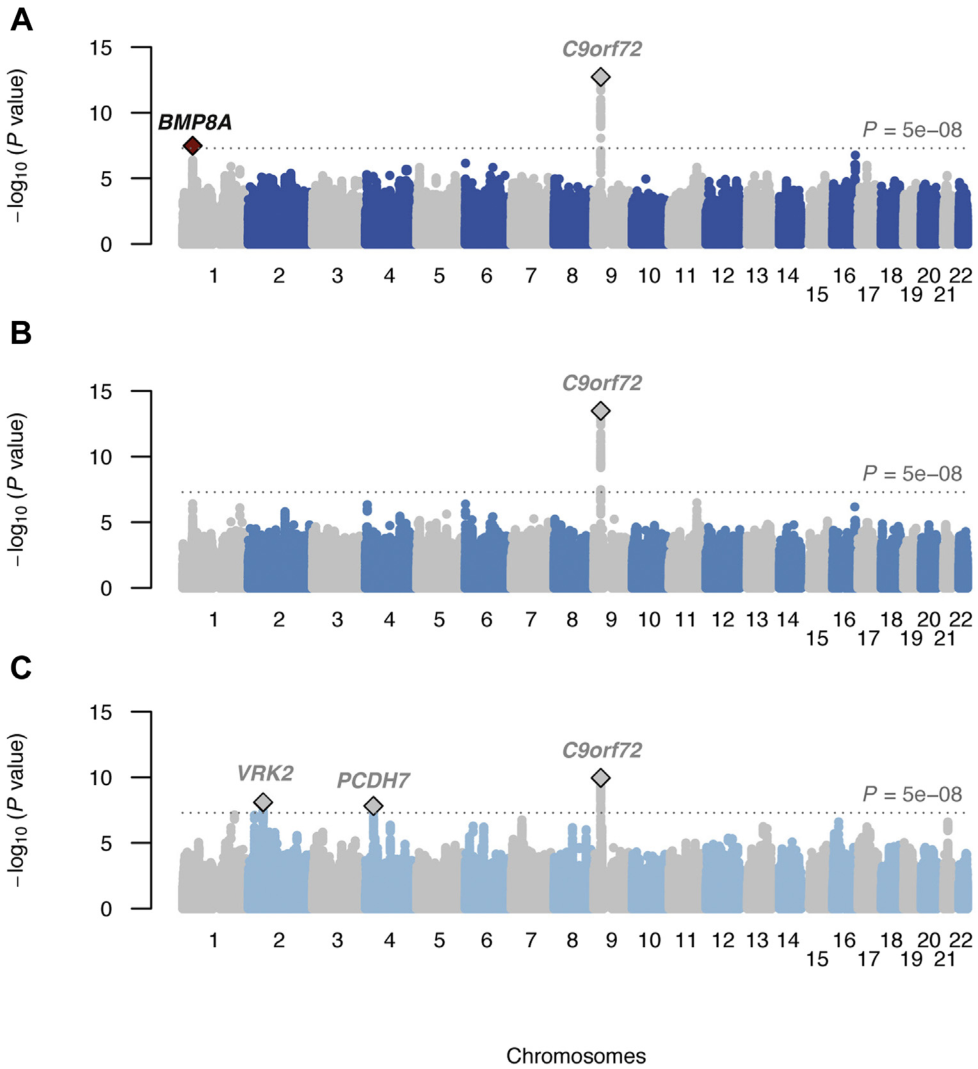

Fig. 3. Association results of ALS epilepsy meta-analyses. Manhattan plots show association $-\log_{10}$-converted p-values (y-axis) of meta-analyzed SNPs against their relative position in the genome (x-axis). Diamonds indicate lead SNPs of loci reaching genome-wide significance, those marked red indicate pleiotropic loci, and those marked gray indicate loci with a stronger association in the single-phenotype GWAS of ALS or epilepsy compared to the meta-analysis. (A) Result for ALS-epilepsy (41,228 controls; 26,634 cases), with a pleiotropic genome-wide significant association (rs61779331, $p = 3.2 \times 10^{-8}$, OR = 1.02) near the gene *BMP8A*. (B) Result for ALS-focal epilepsy (41,228 controls; 21,598 cases). (C) Result for ALS-generalized epilepsy (41,228 controls; 15,808 cases). See Supplementary Table 4A for detailed statistics of lead SNPs. Abbreviations: ALS, amyotrophic lateral sclerosis; GWAS, genome-wide association study; OR, odds ratio; SNP, single-nucleotide polymorphism. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(ILAE) and some of the authors are experts selected by the ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE.

CRediT authorship contribution statement

Dick Schijven: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Remi Stevelink:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Mark McCormack:** Conceptualization, Methodology, Formal analysis, Data curation, Writing - review & editing. **Wouter van Rheenen:** Formal analysis, Data curation, Writing - review & editing. **Jurjen J. Luykx:** Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing. **Bobby P.C. Koeleman:** Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing. **Jan H. Veldink:** Conceptualization, Methodology, Data curation, Writing - original draft, Writing - review & editing.

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We thank the members of the Project MinE ALS GWAS Consortium and the International League Against Epilepsy Consortium on Complex Epilepsies for their contributions (see Supplementary Information for detailed lists of consortium members). This project has received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement n° 772376 - EScORIAL. The collaboration project is co-funded by the PPP Allowance made available by Health~Holland, Top Sector Life Sciences & Health, to stimulate public-private partnerships.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurobiolaging.2020.04.011.

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Supplementary Material

Analysis of shared common genetic risk between amyotrophic lateral sclerosis and epilepsy

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1. Supplementary introduction

Amyotrophic lateral sclerosis (ALS) is characterized by the progressive degeneration of motor neurons. Cramps and fasciculations are common in ALS patients and indicate axonal hyperexcitability in motor neurons (Kanai et al., 2006). Proposed mechanisms for hyperexcitability in ALS include impaired inhibitory signaling through GABAergic interneurons, astrocytes failing to adequately regulate glutamate levels and extracellular K+ concentrations at the synaptic cleft, and altered ion channel expression in motor neurons (Do-Ha et al., 2018). Ion channel dysfunction has been correlated to muscle weakness and motor neuron degeneration (Geevasinga et al., 2015), while peripheral and central hyperexcitability are furthermore strong predictors of shorter survival (Kanai et al., 2012; Shimizu et al., 2018). Similarly, in epilepsy, an imbalance of excitatory and inhibitory mechanisms in the brain contributes to seizure pathogenesis. Interestingly, the anti-epileptic drug retigabine has shown acute beneficial effects on peripheral nerve excitability in ALS (Kovalchuk et al., 2018). Of further note, riluzole – a drug used in the treatment of ALS – has been shown to decrease hippocampal epileptiform activity and reduce seizure activity in epilepsy animal models (Diao et al., 2013; Kim et al., 2007).

Both ALS and epilepsy have been subject of large genome-wide association studies that revealed parts of their heritabilities being explained by common genetic variation, and that discovered genetic loci associated with the risk for these diseases: For ALS, single-nucleotide polymorphism (SNP)-based heritability has been estimated at 8.5% (van Rheenen et al., 2016). In epilepsy, SNP-based heritability estimates ranged from 9.2% for focal epilepsy to as high as 32.1% for generalized epilepsy (The International League Against Epilepsy Consortium on Complex Epilepsies, 2018). In both ALS and epilepsy, several genetic loci reaching genome-wide significant association have been identified (The International League Against Epilepsy Consortium on Complex Epilepsies, 2018; van Rheenen et al., 2016). Previous research has furthermore established genetic overlap between ALS and other neurological diseases, primarily those in the frontotemporal dementia spectrum (Karch et al., 2018).

The beforementioned clinical and preclinical observations and the availability of recent and large genome-wide association study (GWAS) datasets (The International League Against Epilepsy Consortium on Complex Epilepsies, 2018; van Rheenen et al., 2016), showing that the heritability of each of the two diseases is partly explained by common genetic variation, have led us to investigate whether ALS and epilepsy share any common genetic risk.

2. Supplementary methods

2.1 Study population and data

We used individual level data of subjects with European ancestry from recent large GWASs in ALS (N = 12,577 cases; 23,475 controls) (van Rheenen et al., 2016) and epilepsy (N = 14,131 cases; 24,218 controls), including sets of focal (n = 9,095 cases) and generalized (n = 3,305 cases) epilepsy subtypes (The International League Against Epilepsy Consortium on Complex Epilepsies, 2018). Contributors to these studies are listed in the Consortium Members section in this document. Written informed consent was provided by all participants and for both studies local institutional review boards at each contributing site approved study protocols (The International League Against Epilepsy Consortium on Complex Epilepsies, 2018; van Rheenen et al., 2016).

2.2 Genetic correlation analyses

We merged individual-level data of ALS and epilepsy using PLINK (version v1.90b5.4) (Chang et al., 2015), excluded SNPs with a genotype call rate < 0.99, not present in HapMap3 and/or located in the major histocompatibility complex (MHC) region. Genetic relationship matrices (GRMs) were calculated from SNPs in five minor allele frequency (MAF) bins (MAF 0.01-0.10, 0.10-0.20, 0.20-0.30, 0.30-0.40, and 0.40-0.50, frequencies derived from the European subset of 1000 genomes phase 3, 1KG-EUR, n = 503) and all bins combined (MAF 0.01-0.50) using Genome-wide Complex Trait Analysis (GCTA, version 1.91) (Yang et al., 2011). Because of the stronger contribution of SNPs with low MAF to the heritability of ALS (van Rheenen et al., 2016), we used bivariate genetic restricted maximum likelihood (GREML) to calculate genetic correlation (r_g) per MAF bin and on all bins combined in unrelated individuals (GRM off-diagonal < 0.05) and with the first ten genetic principal components (PCs) derived from GRMs included as covariates.

In support of this, we estimated overall genetic correlation from summary-level data using LD score regression (LDSC) with default settings (Bulik-Sullivan et al., 2015). LD scores were calculated in 1 centimorgan windows around SNPs present in HapMap3, using 1KG-EUR as a reference dataset. Summary-level data was merged with HapMap3 and combined association statistics of intersecting SNPs between ALS and epilepsy (including focal and generalized subtypes) with $0.05 \leq \text{MAF} \leq 0.5$ were regressed against LD scores.

2.3 Genomic risk score analyses

Genomic risk scores (GRS) reflect the sum of discovery GWAS SNP effect alleles, weighted for their effect size, in individuals in a target dataset, and can subsequently be tested for association with a target phenotype.

We used the epilepsy mixed linear model (MLM) GWAS results as discovery data and ALS as a target dataset, and vice versa, excluding individuals from the target dataset that were related to individuals used to generate the discovery data (PLINK identity-by-descent PIHAT > 0.10). We excluded variants with a genotype call rate < 0.95 in either the discovery or target dataset. In addition, in the discovery data, we excluded variants other than SNPs, and SNPs with MAF < 0.01, a strand-ambiguous A/T or C/G genotype and those located in genomic regions with a strong or complex LD structure (Supplementary Table 1). LD-independent variants were obtained through clumping of SNPs that intersected with the target dataset, using 1KG-EUR as a reference for LD estimation. Clumping was performed over two rounds: In the first round, SNPs within a 250 kb radius and with an LD R2 > 0.5 relative to a top associated variant were excluded, and in the second round remaining SNPs within a 5000 kb radius and with an LD R2 > 0.2 relative to a top associated variant were removed. Twelve GRS were calculated per individual in the target dataset based on increasing SNP association p-value thresholds (P_T) in the discovery GWAS ($p < 5x10^{-8}$, $p < 5x10^{-7}$, $p < 5x10^{-6}$, $p < 5x10^{-5}$, $p < 5x10^{-4}$, $p < 5x10^{-3}$, $p < 5x10^{-2}$, $p < 0.1$, $p < 0.2$, $p < 0.3$, $p < 0.4$ and $p < 0.5$) using PLINK. GRS were scaled around mean 0 with variance 1 to allow direct comparison of effect sizes between P_Ts. We applied logistic regression, including sex and significant genetic principal components (PCs) (phenotype association $p < 0.05/100 = 0.0005$) as covariates, to test the association between GRS and disease phenotypes and calculate GRS effect estimates on disease liability.

2.4 Meta-analyses

We replicated a previously reported MLM association analysis for ALS using GCTA (van Rheenen et al., 2016), now excluding duplicate and related individuals with the epilepsy data (PLINK PIHAT > 0.10). Inverse-variance weighted fixed effects meta-analyses were performed in METAL for variants with a genotype call rate ≥ 0.95 in MLM GWAS results of ALS and epilepsy (including subtypes) (Willer et al., 2010). Similarly, we performed meta-analyses where we ignored SNP effect direction to discover pleiotropic SNPs with opposing effects in both diseases.

3. Supplementary results

We combined ALS and epilepsy GWAS datasets (totaling 74,401 individuals), applied genetic correlation and GRS analyses to assess shared heritability between these diseases, and performed meta-analyses to discover possible pleiotropic loci.

We found no significant genetic correlations using GCTA-GREML between ALS and epilepsy (r_g = 0.0080 [95% confidence interval -0.079–0.095], p = 0.86), including focal subtype (r_g = 0.052 [-0.046–0.15], p = 0.29) and generalized subtype (r_g = -0.011 [-0.099–0.077], p = 0.81), also when the analysis was additionally stratified on MAF (Figure 1, Supplementary Table 2). The absence of genetic correlation with ALS was confirmed using LDSC for all (r_g = 0.054 [-0.23–0.34], p =0.70), focal (r_g = 0.49 [-0.060–1.04], p = 0.08), and generalized epilepsy (r_g = -0.055 [-0.31–0.20], p = 0.67) (Figure 1). Further analysis with LDSC using available summary-level data from a larger GWAS meta-analysis in ALS (Nicolas et al., 2018), revealed highly similar and non-significant genetic correlation estimates (Supplementary Figure 1). Furthermore, GRS capturing genetic risk for epilepsy were not associated with case-control status in the ALS dataset (Figure 2A, Supplementary Table 3A), and similarly ALS GRS did not associate with epilepsy status (Figure 2B, Supplementary Table 3B).

Inverse-variance weighted meta-analyses of ALS and epilepsy revealed several loci passing the threshold for genome-wide significance (Figure 3, Supplementary Figure 2, Supplementary Table 4A). Only the locus near *BMP8A* in the ALS-epilepsy (all subtypes combined) analysis (Figure 3A) fulfilled criteria for a pleiotropic locus with nominal-significant association p-values ($p < 0.05$) in both studies independently (ALS p = 2.3×10^{-2}, epilepsy p = 8.7×10^{-8}) and a genome-wide significant p-value in meta-analysis (p = 3.2×10^{-8}, OR = 1.02, similar effect directions). This variant, however, was not associated with ALS in a larger GWAS meta-analysis including 20,806 cases and 59,804 controls for which only summary statistics are currently available (p = 0.11, OR [A allele] = 1.03, 95% CI = 0.99-1.06, a corresponding direction of effect compared to the meta-analysis) (Nicolas et al., 2018). For all other loci, the level of association in either ALS or epilepsy alone was higher compared to the combined analysis. In the sign-independent meta-analysis of ALS and generalized epilepsy the signal near *PTPRK* was stronger than both single-trait GWAS (p = 3.5×10^{-10}, Supplementary Figure 3, Supplementary Table 4B), but again the larger GWAS in ALS did not yield a statistically significant association (p = 0.19, OR [T allele] = 1.02, 95% CI = 0.99-1.05, a corresponding direction of effect compared to the ALS MLM result, but opposing direction of effect compared to the epilepsy MLM result) (Nicolas et al., 2018).

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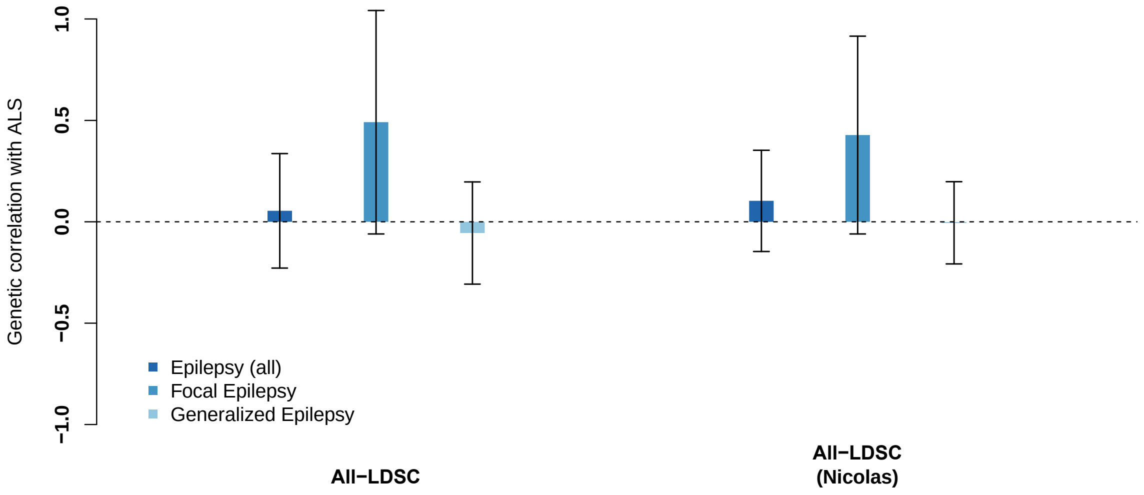
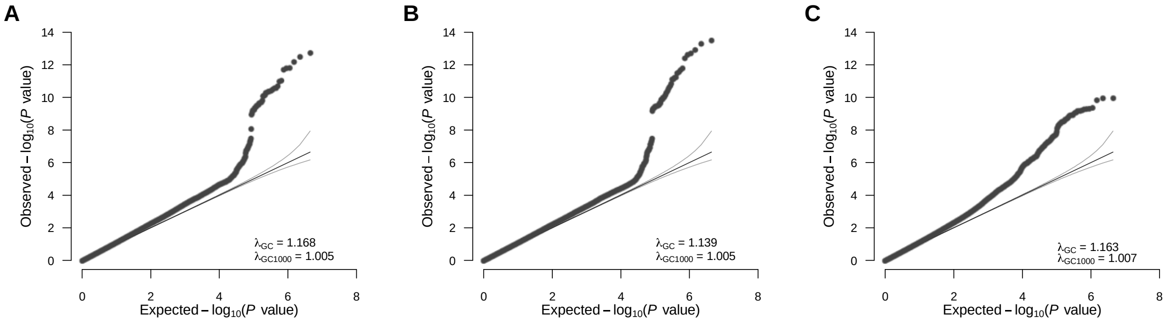
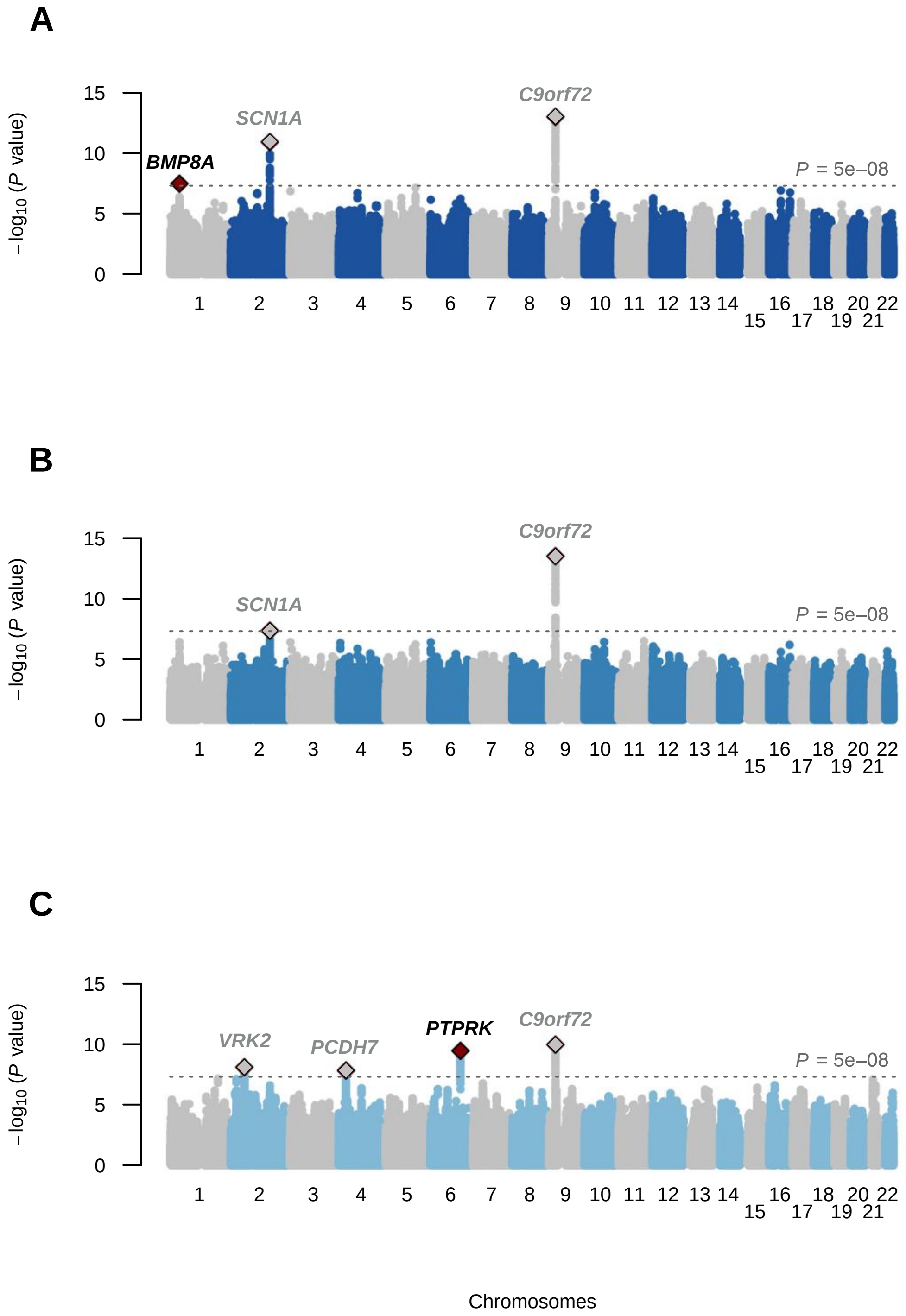
Supplementary Figures



Supplementary Figure 1 LDSC genetic correlation estimates between ALS and epilepsy using ALS GWAS data from van Rheenen *et al.* and Nicolas *et al.* Genetic correlation between ALS and epilepsy (including focal and generalized subtypes) (y-axis) was estimated using LDSC using data from van Rheenen *et al.* (All-LDSC), and Nicolas *et al.* (All-LDSC Nicolas)). Error bars indicate 95% confidence intervals.



Supplementary Figure 2 Observed versus expected association p-values in ALS-epilepsy meta-analyses. Quantile-quantile plots for meta-analyses of **A)** ALS-all epilepsy, **B)** ALS-focal epilepsy, and **C)** ALS-generalized epilepsy. Inflation factor lambda (λ_{GC}), and lambda scaled for a study with 1,000 cases and 1,000 controls (λ_{GC1000}) are shown in each plot.



Supplementary Figure 3 Sign-independent meta-analysis results. Manhattan plots show association -log$_{10}$-converted p-values (y-axis) of meta-analyzed SNPs against their relative position on the genome (x-axis). Diamonds indicate lead SNPs of loci reaching genome-wide significance, those marked red indicate pleiotropic loci, those marked gray indicate loci with a stronger association in the single-phenotype GWAS of ALS or epilepsy compared to the meta-analysis. **A)** Sign-independent meta-analysis of ALS-epilepsy (41,228 controls; 26,634 cases) where the same pleiotropic locus as reported in in Figure 3A was discovered. **B)** Sign-independent meta-analysis of ALS-focal epilepsy (41,228 controls; 21,598 cases). **C)** Sign-independent meta-analysis of ALS-generalized epilepsy (41,228 controls; 15,808 cases) with a pleiotropic association (opposing effect directions between ALS and epilepsy, rs13219424, $p = 3.5 \times 10^{-10}$, OR = 1.02) near the gene *PTPRK*. See Supplementary Table 4 for detailed statistics of lead SNPs.

Supplementary Tables

Supplementary Table 1 Genomic regions of strong LD excluded in genomic risk score calculation

Chromosome	Basepair start	Basepair end
1	48000000	52000000
2	86000000	100500000
	183000000	190000000
3	47500000	50000000
	83500000	87000000
5	44500000	50500000
	129000000	132000000
6	25500000	33500000
	57000000	64000000
	140000000	142500000
7	55000000	66000000
8	8000000	12000000
	43000000	50000000
	8135000	12000000
	112000000	115000000
10	37000000	43000000
11	87500000	90500000
12	33000000	40000000
17	40900000	45000000
20	32000000	34500000

Base pair positions refer to human genome build hg19/GRCh37.

Supplementary Table 2 Results for GREML analysis of ALS and epilepsy subtypes

	h^2 ALS		h^2 Epilepsy			
MAF bin	**Observed scale (SE)**	**Liability scale (SE)**	**Observed scale (SE)**	**Liability scale (SE)**	**cov_g (SE)**	**r_g (SE)**
ALS-All epilepsy						
All	0.024131 (0.001927)	0.051265 (0.004033)	0.057662 (0.002737)	0.125524 (0.005635)	0.000298 (0.001658)	0.007996 (0.044454)
0.01-0.10	0.004253 (0.001212)	0.009036 (0.002573)	0.008871 (0.001635)	0.019312 (0.003547)	0.001345 (0.001001)	0.218974 (0.166300)
0.10-0.20	0.005659 (0.001499)	0.012021 (0.003180)	0.014908 (0.002062)	0.032454 (0.004461)	-0.002193 (0.001252)	-0.238750 (0.139819)
0.20-0.30	0.007977 (0.001525)	0.016946 (0.003232)	0.011688 (0.002048)	0.025444 (0.004440)	-0.000255 (0.001249)	-0.026419 (0.129395)
0.30-0.40	0.003182 (0.001395)	0.006759 (0.002963)	0.013188 (0.002023)	0.028709 (0.004381)	0.000951 (0.001185)	0.146786 (0.184884)
0.40-0.50	0.003510 (0.001231)	0.007456 (0.002614)	0.009251 (0.001767)	0.020138 (0.003835)	0.000442 (0.001045)	0.077637 (0.183738)
ALS-Focal epilepsy						
All	0.024157 (0.001928)	0.051318 (0.004033)	0.047059 (0.002831)	0.107541 (0.006217)	0.001755 (0.001681)	0.052051 (0.049853)
0.01-0.10	0.004266 (0.001212)	0.009063 (0.002573)	0.008475 (0.001749)	0.019369 (0.003985)	0.001038 (0.001035)	0.172609 (0.174416)
0.10-0.20	0.005642 (0.001499)	0.011985 (0.003180)	0.012106 (0.002150)	0.027668 (0.004892)	-0.001526 (0.001279)	-0.184597 (0.157118)
0.20-0.30	0.007999 (0.001526)	0.016993 (0.003232)	0.012514 (0.002166)	0.028599 (0.004926)	0.000427 (0.001286)	0.042652 (0.128468)
0.30-0.40	0.003203 (0.001396)	0.006805 (0.002964)	0.009886 (0.002071)	0.022592 (0.004718)	0.000785 (0.001198)	0.139536 (0.213927)
0.40-0.50	0.003486 (0.001231)	0.007405 (0.002612)	0.004861 (0.001797)	0.011110 (0.004102)	0.000956 (0.001048)	0.232349 (0.258904)
ALS-Generalized epilepsy						
All	0.024125 (0.001927)	0.051253 (0.004033)	0.044636 (0.002124)	0.271195 (0.011908)	-0.000362 (0.001466)	-0.011025 (0.044666)
0.01-0.10	0.004251 (0.001212)	0.009030 (0.002572)	0.005642 (0.001240)	0.034281 (0.007509)	0.001397 (0.000875)	0.285209 (0.184363)
0.10-0.20	0.005665 (0.001499)	0.012035 (0.003180)	0.010549 (0.001591)	0.064102 (0.009598)	-0.001818 (0.001097)	-0.235176 (0.145131)
0.20-0.30	0.008021 (0.001526)	0.017041 (0.003233)	0.007457 (0.001574)	0.045313 (0.009529)	0.000368 (0.001093)	0.047524 (0.141351)
0.30-0.40	0.003088 (0.001394)	0.006560 (0.002961)	0.010714 (0.001590)	0.065101 (0.009582)	0.000236 (0.001055)	0.041081 (0.183603)
0.40-0.50	0.003537 (0.001231)	0.007515 (0.002614)	0.009621 (0.001395)	0.058463 (0.008410)	-0.000302 (0.000930)	-0.051770 (0.159512)

Liability-scale h^2 in ALS was calculated using a prevalence of 0.0025, Liability-scale h^2 in epilepsy was calculated using a prevalence of 0.006 for all epilepsy, 0.003 for focal epilepsy, and 0.002 for generalized epilepsy. MAF, minor allele frequency; h^2, heritability; cov_g, genetic covariance; r_g, genetic correlation; SE, standard error.

Supplementary Table 3 Genomic risk score analysis results

A

	Discovery dataset														
	All Epilepsy					**Focal Epilepsy**					**Generalized Epilepsy**				
P_T	**SNPs**	**OR**	**se**	**Delta R^2**	**p**	**SNPs**	**OR**	**se**	**Delta R^2**	**p**	**SNPs**	**OR**	**se**	**Delta R^2**	**p**
5×10^{-8}	4	0.98	1.2×10^{-2}	1.4×10^{-4}	0.06	1	0.98	1.2×10^{-2}	6.7×10^{-5}	0.20	8	1.01	1.2×10^{-2}	1.1×10^{-5}	0.60
5×10^{-7}	16	1.00	1.3×10^{-2}	1.1×10^{-6}	0.87	3	0.99	1.2×10^{-2}	2.5×10^{-5}	0.43	20	1.01	1.2×10^{-2}	3.3×10^{-5}	0.37
5×10^{-6}	55	1.00	1.3×10^{-2}	1.8×10^{-6}	0.83	30	1.01	1.2×10^{-2}	3.8×10^{-5}	0.33	46	1.00	1.2×10^{-2}	2.6×10^{-6}	0.80
5×10^{-5}	206	1.01	1.3×10^{-2}	1.1×10^{-5}	0.60	156	**1.03**	**1.3×10^{-2}**	**2.4×10^{-4}**	**0.02**	180	1.00	1.3×10^{-2}	2.4×10^{-6}	0.81
5×10^{-4}	1,092	1.00	1.4×10^{-2}	3.1×10^{-7}	0.93	847	1.02	1.3×10^{-2}	7.1×10^{-5}	0.19	799	1.00	1.3×10^{-2}	5.3×10^{-6}	0.72
5×10^{-3}	5,244	0.99	1.6×10^{-2}	1.3×10^{-5}	0.57	4517	1.00	1.5×10^{-2}	4.4×10^{-6}	0.74	4225	1.01	1.4×10^{-2}	2.6×10^{-5}	0.42
5×10^{-2}	24,620	0.99	1.9×10^{-2}	3.7×10^{-6}	0.76	22507	1.02	1.8×10^{-2}	4.5×10^{-5}	0.29	21052	0.99	1.7×10^{-2}	6.0×10^{-6}	0.70
0.1	38,975	1.00	1.9×10^{-2}	6.3×10^{-7}	0.90	36594	1.00	1.8×10^{-2}	5.7×10^{-7}	0.91	34571	0.99	1.7×10^{-2}	3.4×10^{-6}	0.77
0.2	58,330	0.99	2.0×10^{-2}	1.1×10^{-5}	0.61	55623	0.99	1.9×10^{-2}	7.9×10^{-6}	0.66	53535	0.98	1.8×10^{-2}	3.3×10^{-5}	0.37
0.3	72,518	0.99	2.0×10^{-2}	7.7×10^{-6}	0.66	69907	1.00	1.9×10^{-2}	1.6×10^{-6}	0.84	68111	0.98	1.8×10^{-2}	4.8×10^{-5}	0.28
0.4	83,813	0.99	2.0×10^{-2}	6.9×10^{-6}	0.68	81115	1.00	1.9×10^{-2}	3.7×10^{-7}	0.92	79566	0.98	1.8×10^{-2}	4.1×10^{-5}	0.32
0.5	92,480	0.99	2.0×10^{-2}	8.8×10^{-6}	0.64	89911	0.99	1.9×10^{-2}	2.9×10^{-6}	0.79	88794	0.98	1.8×10^{-2}	3.0×10^{-5}	0.39

B

		Target dataset											
		All Epilepsy				**Focal Epilepsy**				**Generalized Epilepsy**			
P_T	**SNPs**	**OR**	**se**	**Delta R^2**	**p**	**OR**	**se**	**Delta R^2**	**p**	**OR**	**se**	**Delta R^2**	**p**
5×10^{-8}	4	1.01	1.2×10^{-2}	5.6×10^{-5}	0.23	1.01	1.3×10^{-2}	7.7×10^{-6}	0.69	1.04	2.0×10^{-2}	2.9×10^{-2}	0.05
5×10^{-7}	8	1.01	1.2×10^{-2}	1.3×10^{-5}	0.57	1.00	1.3×10^{-2}	5.2×10^{-6}	0.74	**1.05**	**2.0×10^{-2}**	**4.2×10^{-2}**	**0.02**
5×10^{-6}	17	1.02	1.2×10^{-2}	6.6×10^{-5}	0.19	1.00	1.3×10^{-2}	1.0×10^{-6}	0.89	**1.06**	**2.0×10^{-2}**	**7.2×10^{-2}**	**0.002**
5×10^{-5}	86	0.99	1.2×10^{-2}	7.6×10^{-6}	0.66	0.98	1.3×10^{-2}	8.4×10^{-5}	0.19	1.04	2.0×10^{-2}	2.9×10^{-2}	0.05
5×10^{-4}	483	0.99	1.3×10^{-2}	1.6×10^{-5}	0.53	0.99	1.4×10^{-2}	2.6×10^{-5}	0.46	1.01	2.1×10^{-2}	5.4×10^{-4}	0.79
5×10^{-3}	2,836	0.99	1.4×10^{-2}	1.4×10^{-5}	0.56	0.99	1.6×10^{-2}	3.2×10^{-5}	0.42	0.99	2.4×10^{-2}	7.5×10^{-4}	0.75
5×10^{-2}	17,125	0.97	1.9×10^{-2}	7.9×10^{-5}	0.16	0.96	2.1×10^{-2}	1.6×10^{-4}	0.07	1.01	3.2×10^{-2}	7.0×10^{-4}	0.76
0.1	28,319	0.99	2.0×10^{-2}	2.1×10^{-5}	0.46	0.98	2.2×10^{-2}	4.3×10^{-5}	0.35	1.01	3.4×10^{-2}	5.7×10^{-4}	0.78
0.2	46,467	0.99	2.1×10^{-2}	2.8×10^{-6}	0.79	1.00	2.3×10^{-2}	1.7×10^{-6}	0.85	1.02	3.5×10^{-2}	1.9×10^{-3}	0.62
0.3	60,997	0.98	2.1×10^{-2}	2.9×10^{-5}	0.39	0.99	2.4×10^{-2}	1.0×10^{-5}	0.65	0.99	3.6×10^{-2}	2.7×10^{-4}	0.85
0.4	73,344	0.98	2.1×10^{-2}	3.7×10^{-5}	0.33	0.98	2.4×10^{-2}	2.5×10^{-5}	0.47	1.00	3.6×10^{-2}	3.0×10^{-5}	0.95
0.5	83,607	0.98	2.1×10^{-2}	4.4×10^{-5}	0.29	0.98	2.4×10^{-2}	3.5×10^{-5}	0.40	0.99	3.6×10^{-2}	1.9×10^{-4}	0.88

A Results using epilepsy (including subtypes) as discovery datasets and ALS as a target dataset. Explained variance in ALS (case-control status) by epilepsy GRSs was tested using logistic regression, including sex and significant principal components ($p < 0.05/100 = 5 \times 10^{-4}$; PCs 1, 2, 3, 5, 12, 17, 18, 19, 21, 26, 28, 29, 33, 43, 45, 46, 47, 53, 65, 70, 75, 96) as covariates.

B Results using ALS as discovery dataset and epilepsy (including subtypes) as a target dataset. Explained variance in epilepsy (case-control status) by ALS GRSs was tested using logistic regression, including sex and significant principal components ($p < 0.05/100 = 5 \times 10^{-4}$; all epilepsy: PCs 1, 2, 3, 6, 7, 22, 24, 31, 95; focal epilepsy: PCs 1, 2, 3, 6, 7, 8, 22, 24, 31; generalized epilepsy: PCs1, 2, 3, 7, 8, 9, 24, 44, 66, 95) as covariates.

GRSs were scaled around mean 0 with variance 1. OR reflects the odds for disease per one unit (one SD) increase of the GRS at the respective P_T.

Table columns: P_T, p-value threshold of SNP association in discovery data; SNPs, number of SNPs in P_T (in B this is the maximum number of SNPs due to missing SNP genotypes; OR, odds ratio of the GRS; se, standard error of the effect estimate of the GRS; Delta R^2, difference in explained variance (Nagelkerke R^2) compared to baseline model without GRS; p, p-value of the GRS in the model.

Results in bold show GRS effects with $p < 0.05$, although none survived multiple-testing correction (Bonferroni-correction for four traits times twelve P_T included, $p < 0.001$).

Supplementary Table 4 Meta-analysis association results of lead SNPs

A. Normal meta-analysis

Chr	bp	SNP	Risk allele	ALS OR	se	p	Epilepsy OR	se	p	Meta-analysis OR	se	p	Direction
ALS-All epilepsy													
1	***39970928***	***rs61779331***	***A***	***1.01***	***4.6 x 10^{-3}***	***2.3 x 10^{-2}***	***1.02***	***4.0 x 10^{-3}***	***8.7 x 10^{-8}***	***1.02***	***3.0 x 10^{-3}***	***3.2 x 10^{-8}***	**++**
9	27545467	rs812858	T	1.05	4.6 x 10^{-3}	1.2 x 10^{-24}	1.00	4.1 x 10^{-3}	4.7 x 10^{-1}	1.02	3.1 x 10^{-3}	1.8 x 10^{-13}	++
ALS-Focal epilepsy													
9	27545467	rs812858	T	1.05	4.6 x 10^{-3}	1.2 x 10^{-24}	1.00	4.1 x 10^{-3}	3.1 x 10^{-1}	1.02	3.1 x 10^{-3}	3.2 x 10^{-14}	++
ALS-Generalized epilepsy													
2	58042241	rs1402398	G	1.00	4.0 x 10^{-3}	0.54	1.02	2.7 x 10^{-3}	6.0 x 10^{-11}	1.01	2.3 x 10^{-3}	8.0 x 10^{-9}	++
4	31148846	rs1463849	G	1.00	4.0 x 10^{-3}	0.27	1.02	2.7 x 10^{-3}	9.3 x 10^{-10}	1.01	2.3 x 10^{-3}	1.5 x 10^{-8}	++
9	27545960	rs700791	A	1.05	4.6 x 10^{-3}	1.2 x 10^{-24}	1.00	3.3 x 10^{-3}	5.2 x 10^{-1}	1.02	2.7 x 10^{-3}	1.1 x 10^{-10}	++

B. Sign-independent meta-analysis

Chr	Bp	SNP	Alleles	p ALS	p Epilepsy	Meta-analysis OR	se	p
ALS-All epilepsy								
1	39970928	rs61779331	A/C	2.3 x 10^{-2}	8.7 x 10^{-8}	1.02	3.00 x 10^{-3}	3.19 x 10^{-8}
2	166998767	rs6432877	C/G	8.0 x 10^{-2}	8.9 x 10^{-14}	1.02	3.00 x 10^{-3}	1.14 x 10^{-11}
9	27563755	rs2484319	A/C	1.9 x 10^{-26}	0.57	1.02	3.00 x 10^{-3}	9.40 x 10^{-14}
ALS-Focal epilepsy								
2	166998767	rs6432877	C/G	8.0 x 10^{-2}	8.9 x 10^{-14}	1.02	3.00 x 10^{-3}	4.46 x 10^{-8}
9	27545467	rs812858	C/T	1.2 x 10^{-24}	0.31	1.02	3.10 x 10^{-3}	3.15 x 10^{-14}
ALS-Generalized epilepsy								
2	58042241	rs1402398	A/G	0.54	6.0 x 10^{-11}	1.01	2.30 x 10^{-3}	7.94 x 10^{-9}
4	31148846	rs1463849	A/G	0.27	9.3 x 10^{-10}	1.01	2.30 x 10^{-3}	1.48 x 10^{-8}
6	***128332084***	***rs13219424***	***T/C***	***7.3 x 10^{-3}***	***7.9 x 10^{-9}***	***1.02***	***2.40 x 10^{-3}***	***3.50 x 10^{-10}***
9	27497988	rs10967965	A/T	8.3 x 10^{-22}	0.28	1.02	2.70 x 10^{-3}	1.08 x 10^{-10}

Table columns: Chr: chromosome; bp: basepair position (hg19/GRCh37); SNP: variant rs-number; Risk allele: disease-associated allele; OR: odds ratio of SNP in ALS, epilepsy and meta-analysis; se: standard error of SNP effect estimate in ALS, epilepsy and meta-analysis; p: association p-value of SNP in ALS, epilepsy and meta-analysis; Direction: direction of effect in ALS and epilepsy. Pleiotropic loci are highlighted.

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