Dissecting the Shared Genetic Architecture of Common Epilepsies With Cortical Brain Morphology

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Abstract

Background and Objectives
Epilepsies are associated with differences in cortical thickness (TH) and surface area (SA). However, the mechanisms underlying these relationships remain elusive. We investigated the extent to which these phenotypes share genetic influences.

Methods
We analyzed genome-wide association study data on common epilepsies (n = 69,995) and TH and SA (n = 32,877) using Gaussian mixture modeling MiXeR and conjunctional false discovery rate (conjFDR) analysis to quantify their shared genetic architecture and identify overlapping loci. We biologically interrogated the loci using a variety of resources and validated in independent samples.

Results
The epilepsies (2.4 k–2.9 k variants) were more polygenic than both SA (1.8 k variants) and TH (1.3 k variants). Despite absent genome-wide genetic correlations, there was a substantial genetic overlap between SA and genetic generalized epilepsy (GGE) (1.1 k), all epilepsies (1.1 k), and juvenile myoclonic epilepsy (JME) (0.7 k), as well as between TH and GGE (0.8 k), all epilepsies (0.7 k), and JME (0.8 k), estimated with MiXeR. Furthermore, conjFDR analysis identified 15 GGE loci jointly associated with SA and 15 with TH, 3 loci shared between SA and childhood absence epilepsy, and 6 loci overlapping between SA and JME. 23 loci were novel for epilepsies and 11 for cortical morphology. We observed a high degree of sign concordance in the independent samples.

Discussion
Our findings show extensive genetic overlap between generalized epilepsies and cortical morphology, indicating a complex genetic relationship with mixed-effect directions. The results suggest that shared genetic influences may contribute to cortical abnormalities in epilepsies.

Introduction

Epilepsies, defined by recurrent seizures, are a heterogeneous group of neurologic disorders that affect approximately 1% of the global population[1] and are associated with considerable disability and morbidity.[2] The underlying pathogenesis of epilepsies is poorly understood, and

Glossary

AIC = Akaike information criterion; **CAE** = childhood absence epilepsy; **condFDR** = conditional false discovery rate; **conjFDR** = conjunctional false discovery rate; **FDR** = false discovery rate; **GGE** = genetic generalized epilepsy; **GWAS** = genome-wide association studies; **ILAE** = International League Against Epilepsy; **JME** = juvenile myoclonic epilepsy; **LDSC** = linkage disequilibrium score regression; **MHC** = major histocompatibility complex; **SA** = surface area; **TH** = cortical thickness; **V2G** = Variant to Gene.

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the presently available treatments are inadequate for many patients.[3] Epilepsies are classified by onset into 2 main groups: focal epilepsies and genetic generalized epilepsies (GGEs),[4] both of which are associated with widespread structural brain abnormalities beyond the epileptogenic focus.[5-7] While lower cortical thickness (TH) has been associated with both focal epilepsies and GGEs, there are also regional differences across epilepsy subtypes.[7] Differences in cortical surface area (SA) may also vary across epilepsy subtypes and cortical regions. Smaller regional SA has been reported for several epilepsies, although these findings cannot be generalized across all epilepsies.[8-11] Furthermore, the extent to which these cortical differences are part of epileptogenesis, represent consequences of epileptic seizures, or environmental factors such as medication use remains elusive.[7,12]

Studying the genetic relationship between epilepsies and cortical morphology may offer new insights into their shared causative factors. Furthermore, genomic studies may inform the development of new diagnostic and therapeutic approaches and improve clinical practice by facilitating genomic precision medicine. TH, SA,[13] and common epilepsies are heritable, although the heritability estimates vary across epilepsy subtypes.[14] Large-scale genome-wide association studies (GWAS) have reported hundreds of genetic loci associated with TH and with SA.[13,15-17] While SA has been associated with variants contributing to fetal development such as gene regulation in neural progenitor cells, TH has been associated with variants influencing regulation of biological processes in the adult human brain such as myelination, suggesting partially distinct genetic underpinnings underlying SA and TH.[13] Moreover, GWAS on epilepsies have identified more than 60 genetic risk loci to date.[14,18,19] Of interest, a polygenic risk score study for focal epilepsies and GGEs found a weak positive association with cortical morphology,[20] suggesting shared genetic effects. By contrast, a recent study analyzing larger GWAS data reported no significant genetic correlations between common epilepsies and TH or SA.[21] However, a genetic correlation assumes consistent allelic effect directions between 2 traits, which is not always the case with polygenic complex phenotypes that often have a shared genetic architecture with mixed effect directions.[22] Thus, genetic overlap can be present in the absence of genetic correlations in a scenario of mixed allelic effect directions among the shared variants,[23-25] as recently shown between common epilepsies and psychiatric disorders.[19]

To investigate the genetic relationship between common epilepsies and TH and SA, we here analyzed large GWAS data

sets using the biostatistical tools MiXeR and conjunctional false discovery rate (ConjFDR). MiXeR[26] estimates the number of causal variants contributing to each trait and quantifies the polygenic overlap between 2 traits regardless of genetic correlations. Moreover, conjFDR analysis enhances genetic discovery of shared genomic loci[22,27] and has identified a substantial amount of genetic variants shared between multiple complex human traits in recent years irrespective of their effect directions.[19,24,25,28,29]

Methods

Sample Description

Discovery Samples

We acquired GWAS summary statistics data based on the largest available samples, all of European ancestry (Table 1). The data for epilepsies[14] were obtained from the International League Against Epilepsy (ILAE) Consortium for the broad phenotypes all epilepsies, focal epilepsies, and GGEs, including the focal subtypes lesion negative focal epilepsy, focal epilepsy with hippocampal sclerosis, and focal epilepsy with lesions other than hippocampal sclerosis and the generalized subtypes childhood absence epilepsy (CAE), juvenile absence epilepsy, juvenile myoclonic epilepsy (JME), and generalized tonic-clonic seizures.

We obtained T1-weighted MRI neuroimaging data from the UK Biobank under the accession number 27412 and generated GWAS data on average TH and total SA based on Freesurfer v5.3 recon-all cortical pipeline[30] after excluding individuals with poor scan quality. We also excluded individuals with neurologic, psychiatric, or brain-related conditions, specifically the diagnoses C69-C72, F00-F99, G00-G99, I60-I69, and Q00-07 from the ICD10. For conducting association analysis, age, sex, scan quality, scanner location, and the first 20 genetic principal components were included as covariates, and a rank-base inverse normal transformation was applied. The summary statistics were then generated using the standard additive model of linear association in REGENIE v3.2.5.[31] All GWAS summary statistics underwent quality control and were formatted with the cleansumstats pipeline v1.6.0.[32]

Independent Samples

We used GWAS summary statistics from independent cohorts to test the validity of our findings (Table 1). All independent samples are of European ancestry, consistent with the

Table 1 Summary Data From All GWAS Used in This Study

Phenotype	Sample size, n	SNPs, n	Source
Discovery samples			
All epilepsy	27,559 cases, 42,436 controls	4,137,194	ILAE[14]
Focal epilepsies	14,939 cases, 42,436 controls	4,121,249	ILAE[14]
Genetic generalized epilepsies	6,952 cases, 42,436 controls	4,123,710	ILAE[14]
Focal epilepsy with hippocampal sclerosis (HS)	1,260 cases, 42,436 controls	3,900,814	ILAE[14]
Lesion negative focal epilepsy	5,778 cases, 42,436 controls	3,975,365	ILAE[14]
Focal epilepsy with lesions other than HS	4,213 cases, 42,436 controls	4,006,969	ILAE[14]
Childhood absence epilepsy	1,049 cases, 42,436 controls	4,220,933	ILAE[14]
Juvenile absence epilepsy	662 cases, 42,436 controls	4,225,222	ILAE[14]
Juvenile myoclonic epilepsy	1,732 cases, 42,436 controls	4,223,181	ILAE[14]
Generalized tonic-clonic seizures	485 cases, 42,436 controls	4,214,303	ILAE[14]
Cortical surface area	32,877	12,322,315	UK Biobank
Cortical thickness	32,877	12,322,315	UK Biobank
Independent samples			
All epilepsy	11,740 cases, 287,837 controls	14,614,037	FinnGen (R9)
Cortical surface area	23,909	6,776,173	ENIGMA[13]
Cortical thickness	23,909	6,816,621	ENIGMA[13]

discovery samples. The sample for epilepsies (G6_EPLEPSY) was obtained from FinnGen (r9) and includes all epilepsies as a combined phenotype.[33] The GWAS summary statistics for SA and TH were obtained from independent cohorts from the ENIGMA consortium, excluding UK Biobank.[13]

Standard Protocol Approvals, Registrations, and Patient Consents

All GWAS investigated in this study were approved by the relevant ethics committees, and informed consent was obtained from all participants. The Regional Committee for Medical and Health Research Ethics for the South-East Norway has evaluated the current protocol and found that no additional institutional review board approval was needed. We adhered to STREGA reporting guidelines when preparing this article.[34]

Data Analysis

Filtering of Summary Statistics

For all analyses, we excluded SNPs around the extended major histocompatibility complex (MHC) region, chromosome 8p23.1, and *MAPT* region (genome build GRCh37/hg19 locations chr6:25119106-33854733; chr8:7200000-12500000; chr17:40000000-47000000, respectively) and SNPs in linkage disequilibrium (LD) ($r^2 > 0.1$) with these regions before fitting the statistical models to avoid LD inflation in our analyses.[35] The average empirical distribution function was obtained by random selection of SNPs in each LD block ($r^2 > 0.1$) with 500 iterations.

Genetic Correlations

Pairwise genetic correlations (r_g) were computed using linkage disequilibrium score regression (LDSC).[36] LDSC estimates genetic correlations at the genome-wide level. LDSC was developed as a tool to distinguish between the contributions from polygenic effects and from confounding factors. Genetic correlations are estimated contingent on the deviation between chi-square statistics and expected values under the null hypothesis. Multiple testing correction was applied by using the Benjamini-Hochberg method (q < 0.05).

Gaussian Causal Mixture Models

We applied univariate and bivariate Gaussian causal mixture models to GWAS summary statistics using MiXeR (v1.3).[26] Using maximum likelihood estimation, univariate MiXeR estimates the number of causal variants explaining 90% of SNP heritability (polygenicity) as the distribution of SNPs with non-zero additive genetic effects beyond LD and discoverability as the variance of effect sizes of the SNPs with non-zero effects. The SNP heritability is then estimated on the observed scale based on the polygenicity and discoverability estimates. Next, bivariate MiXeR estimates the number of shared and non-overlapping causal variants between 2 traits.

All point estimates and standard deviations were obtained by performing 20 iterations with 2 million random SNPs, followed by random pruning at a coefficient of determination (r^2) threshold of 0.8 (i.e., ~600K SNPs per iteration). Akaike

information criterion (AIC) was used to evaluate the model fit. For more information on MiXeR, see the original publication.[26]

Conjunctional False Discovery Rate Analysis

We used the conjFDR implemented in the pleioFDR software tool to boost the discovery of shared genomic loci associated with epilepsies and cortical morphology.[22,27] The conjFDR method is an extension to the conditional false discovery rate (condFDR), which rearranges the test statistics in a primary trait (e.g., GGE) by conditioning on SNP associations with a secondary trait (e.g., SA). The conjFDR method performs 2 condFDR analyses by first conditioning on the first trait and then conditioning on the second trait and selects the maximum of the 2 condFDR values as the conjFDR value. The conjFDR threshold of 0.05 was used in line with previous literature.[22,27]

The cross-trait enrichment is plotted using conditional Q-Q plots, which depict p-value distributions for a primary trait for all SNPs and for SNP strata set by their association with a secondary trait. A leftward deflection in the Q-Q plots from the null hypothesis (diagonal) with a decrease in p-values signifies strong cross-trait enrichment. For detailed information on condFDR/conjFDR, see the original publications.[22,27]

Sign Concordance Analysis

For validation, we tested our findings for sign concordance in independent samples.[37] Sign concordance test compares the overall pattern of concordance of allelic effect directions of the lead SNPs between the discovery and independent samples. To secure a sufficient number of variants for valid analysis, we pooled all lead SNPs from epilepsy phenotypes (GGE, CAE, and JME). To determine the number of lead SNPs in the shared loci with consistent allelic effect directions in the discovery and independent samples, we compared the point estimate of the beta coefficients. Assuming the null hypothesis that there is no genetic association with the trait of interest, the likelihood of randomly observing sign concordance stands at 50%. We evaluated whether the observed sign concordance rates were significantly higher than expected by chance (50%) by conducting a two-tailed exact binomial test.

Functional Analyses

Genomic Loci Definition

Independent genomic loci were defined by establishing independent significant SNPs as $r^2 < 0.60$ and conjFDR <0.05 according to the FUMA protocol.[38] Lead SNPs were then defined by the independent significant SNPs with $r^2 < 0.1$ in approximate LD. Candidate SNPs were selected as conjFDR <0.10 and in LD ($r^2 > 0.60$) with an independent significant SNP. Loci within >250 kb were merged, and the lead SNP of the merged locus was selected as the SNP with the most significant conjFDR value. The loci borders were set by identifying all candidate SNPs in LD ($r^2 \geq 0.6$) with one of the independent significant SNPs in the locus. All LD r^2 values were obtained from the 1000 Genomes Project European-ancestry haplotype reference panel.[39]

The concordance effects of the shared loci were evaluated by studying their z-scores and odds ratios. Novel loci were identified as loci not within 500 kb of the reported loci from the original GWAS or not listed by the GWAS Catalog[40] or Genes4Epilepsy[41] or other GWAS analyses on epilepsies or average TH or total SA.

Functional Annotation

All candidate SNPs were functionally annotated with combined annotation-dependent depletion (CADD) scores to predict deleterious SNP effects on proteins, regulomeDB scores to predict the likelihood of regulatory function of a SNP, and chromatin state scores to predict transcriptional effects. The lead SNPs were mapped to putative causal genes using the Variant to Gene (V2G) tool from the open-source OpenTargets Genetics.[42] For gene mapping, V2G uses physical proximity of SNPs to genes, molecular phenotype quantitative trait loci investigations, and chromatin interaction where 3D DNA-DNA interactions are considered. V2G leverages this information in machine learning algorithms on the input of lead SNPs. Hypergeometric tests for gene expression and gene-set analysis of the identified genes from V2G were performed using FUMA and Genotype-Tissue Expression data.[43,44]

Data Availability

GWAS summary statistics used in this study are publicly available and can be accessed through the original publications. MiXeR (github.com/precimed/mixer). CondFDR and ConjFDR (github.com/precimed/pleiofdr). LDSC (github.com/bulik/ldsc, github.com/comorment/ldsc). FUMA (fuma.ctglab.nl/). OpenTargets Genetics (genetics.opentargets.org/). REGENIE (github.com/rgcgithub/regenie). Cleansumstats (github.com/BioPsyk/cleansumstats)

Results

Genetic Correlations

We evaluated pairwise genome-wide genetic correlations across all phenotypes using LDSC[36] (eTable 1). We found no significant genetic correlations for any of the epilepsies with TH and SA, in line with previous findings.[21] Furthermore, we found TH and SA to be significantly negatively correlated with each other ($r_g = -0.35$, $p = 3.61 \times 10^{-15}$). Almost all epilepsies were significantly positively correlated with each other, although correlations for GGEs did not show significance with focal epilepsies with hippocampal sclerosis or with focal epilepsies with other lesions. Owing to low sample sizes, analyses with juvenile absence epilepsy and generalized tonic-clonic seizures lack sufficient power and, therefore, should be interpreted with caution.

Gaussian Causal Mixture Models

Univariate MiXeR

Univariate MiXeR analyses had sufficient power only for all epilepsy, GGE, JME, SA, and TH as indicated by positive AIC

scores (eTable 2). The epilepsies were estimated to be more polygenic than SA and TH. Specifically, we estimated that 1.3 k (SD = 0.10 k) causal variants influence TH, 1.8 k (SD = 0.13 k) causal variants influence SA, 2.5 k (SD = 0.29 k) causal variants influence JME, 2.9 k (SD = 0.23 k) causal variants influence GGE, and 2.9 k (SD = 0.38 k) causal variants influence all epilepsy. The trait with highest discoverability (σ_β^2 = 4.73 × 10^{-4}, SD = 4.50 × 10^{-5}) and heritability (h^2 = 0.76, SD = 0.04) was JME, whereas all epilepsy was the trait with lowest discoverability (σ_β^2 = 4.31 × 10^{-5}, SD = 5.72 × 10^{-6}) and heritability (h^2 = 0.08, SD = 3.63 × 10^{-2}) among the tested phenotypes.

Bivariate MiXeR

In the bivariate analyses, we uncovered the degree of overlapping genetic architecture and found a consistent pattern of genetic overlap between epilepsies (GGE, JME, and all epilepsy) and cortical morphology (SA and TH) (Figure 1, eTables 3–4). We estimated 1.1 k (SD = 0.20 k) variants shared between SA and GGE, 1.1 k (SD = 0.42 k) variants shared between SA and all epilepsy, and 0.7 k (SD = 0.25 k) variants shared between SA and JME. Furthermore, we estimated 0.8 k (SD = 0.14 k) variants shared between TH and GGE, 0.7 k (SD = 0.27 k) variants shared between TH and all epilepsy, and 0.8 k (SD = 0.20 k) variants shared between TH and JME. The fraction of the concordant variants within the shared variants was 46% for SA and GGE (SD = 0.02), 49% for SA and all epilepsy (SD = 0.02), and 48% for SA and JME (SD = 0.02) and 51% for TH and GGE (SD = 0.01), 43% for TH and all epilepsy (SD = 0.04), and 49% for TH and JME (SD = 0.01), underlining the mixed effect directions of the shared variants. Like univariate analyses, GWAS on other epilepsies had insufficient power for bivariate analysis as indicated by negative AIC scores.

Conjunctional FDR Analysis

In line with the MiXeR estimates of overlap, we observed cross-trait enrichment between GGE and SA and TH using Q-Q plots (eFigure 2). In addition, we also observed cross-trait enrichment between SA, CAE, and JME. No cross-trait enrichment was observed neither for all epilepsy nor for other epilepsies with any of the cortical phenotypes.

We then leveraged the observed cross-trait enrichment between epilepsies and cortical morphology to identify shared loci using conjFDR analysis (eTables 5–8). At conjFDR <0.05, we identified 15 loci jointly associated with GGE and SA and 15 loci jointly associated with GGE and TH, where 2 loci at chromosomes 2 (near *LINC01965*) and 6 (the MHC region) were identified in both analyses. Moreover, we identified 3 loci shared between CAE and SA and 6 loci shared between JME and SA, in which one locus at chromosome 8 (near *FAM49B*) was jointly associated with CAE, JME, and SA. We also identified 4 loci shared between GGE, JME, and SA, of which 2 loci were further shared between GGE and TH and SA. A total of 28 loci were identified for GGE, 6 for JME, 3 for CAE, 15 for SA, and 15 for TH. Among these, 20 were

Figure 1 Genome-Wide Genetic Overlap and Genetic Correlations Between Cortical Morphology (SA, TH) and Epilepsies (All Epilepsy, GGE, JME)
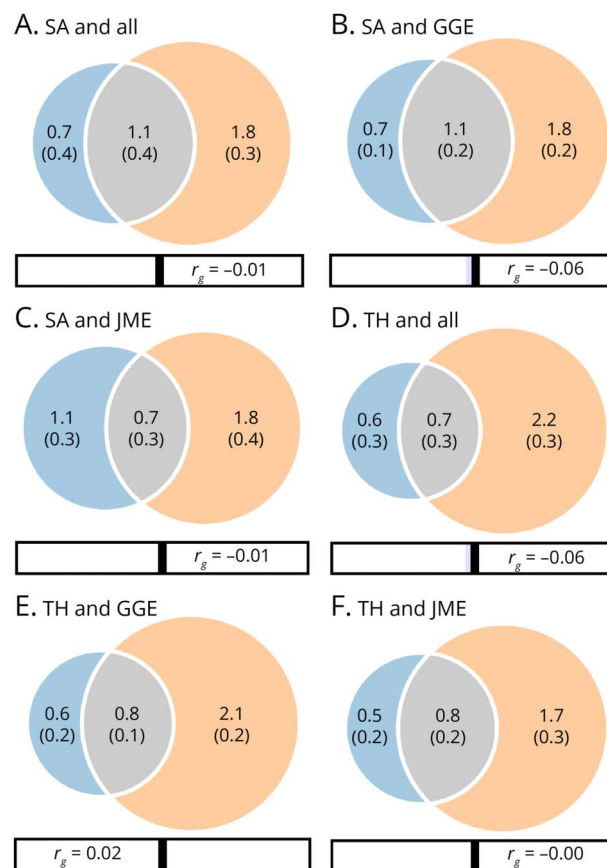
The numbers in the Venn diagrams represent the number of shared and phenotype-specific trait-influencing variants which account for 90% of SNP heritability in thousands, and r_g represents genome-wide genetic correlations. All = all epilepsies; GGE = genetic generalized epilepsy; JME = juvenile myoclonic epilepsy; SA = total cortical surface area; TH = average cortical thickness.

novel loci for GGE, 2 novel loci for JME, 2 novel loci for CAE, 7 novel loci for SA, and 4 novel loci for TH.

We also evaluated the effect directions of the lead SNPs for each shared locus. Among the loci shared between GGE and SA, 8 of 15 lead SNPs had the same allelic effect directions. Similarly, 7 of 15 lead SNPs shared between GGE and TH had the same allelic effect directions. All of the lead SNPs shared between CAE and SA had opposite allelic effect directions while 4 of 6 lead SNPs shared between JME and SA had opposite allelic directions.

Sign Concordance Test

For epilepsies combined (GGE, CAE, and JME), 27 of 38 lead SNPs (71%) with conjFDR <0.05 were sign concordant in the discovery and independent samples (binomial test p = 6.93 × 10^{-3}). For SA, 18 of 23 lead SNPs (78%) with conjFDR <0.05 were sign concordant (p = 5.31 × 10^{-3}). Finally, for TH, 13 of 15 lead SNPs (87%) were sign concordant (p = 3.69 × 10^{-3}) (eTable 9).

Functional Annotation

Functional annotation of the candidate SNPs revealed that the majority are located in intronic and intergenic regions (eTables 10–13). There was a total of 10 nonsynonymous exonic variants, which were detected within 7 loci implicating the genes *ELL2*, *PRRC2A*, *DDN*, *EFS*, *ULK3*, *CDK5RAP3*, *UPK1A*, and *KMT2B* (eTable 14). Across the analyses, 14 candidate SNPs had a CADD score higher than 12.37, which is a sign of deleteriousness.[45] For gene mapping, we used OpenTargets[42] and assigned genes to lead SNPs based on their Variant-to-Gene (V2G) score (eTables 15–18). The gene-set analyses for individual and combined analyses were underpowered and did not yield any significantly enriched gene-sets for the genes mapped to the loci shared between generalized epilepsies and cortical morphology phenotypes.

Discussion

In this study, we leveraged recent large-scale GWAS data to elucidate the shared genetic architecture of common epilepsies and cortical morphology using the statistical tools MiXeR and conjFDR. Despite a lack of genome-wide genetic correlations, we found substantial genetic overlap between the phenotypes, contrasting previous work.[21] Furthermore, using conjFDR, we identified 32 distinct loci jointly associated with generalized epilepsies (GGE, JME, and CAE) and cortical morphology (Figure 2, A and B). Among these, 23 loci were novel for epilepsies and 7 and 4 were novel for SA and TH, respectively (eTables 5–8). Altogether, our study demonstrated that common epilepsies and cortical morphology partly share a common genetic basis, involving a mixture of effect directions across the shared variants, indicating a complex genetic relationship.

We estimated that the genetic architecture of epilepsies is approximately 1.5 times more polygenic than the brain structure traits, using MiXeR. The larger number of common genetic variants involved in the epilepsies may indicate a more complex genetic architecture (Figure 1, eTables 2–4). Accordingly, the observed overlap constitutes a larger fraction of the genetic architectures of SA and TH than of the epilepsies. The presence of substantial genetic overlap in the absence of significant genetic correlations is in line with findings of extensive pleiotropy of common variants with mixed effect directions across a range of complex phenotypes.[19,24,25,28] This has also been demonstrated for cortical morphology and epilepsies vs other phenotypes.[19,24] Furthermore, the indications of genetic overlap with mixed effect directions was observed using both MiXeR and conjFDR, and the high degree of sign concordance in the independent samples (eTable 9) supports the validity of the results. Overall, these findings of mixed effect directions do not imply a concordance in genetic variants influencing epilepsy risk and cortical brain formation but are in line with the complex relationships between TH, SA, and epilepsies, which vary across epilepsy subtypes and cortical regions.[8-11] Future investigations should
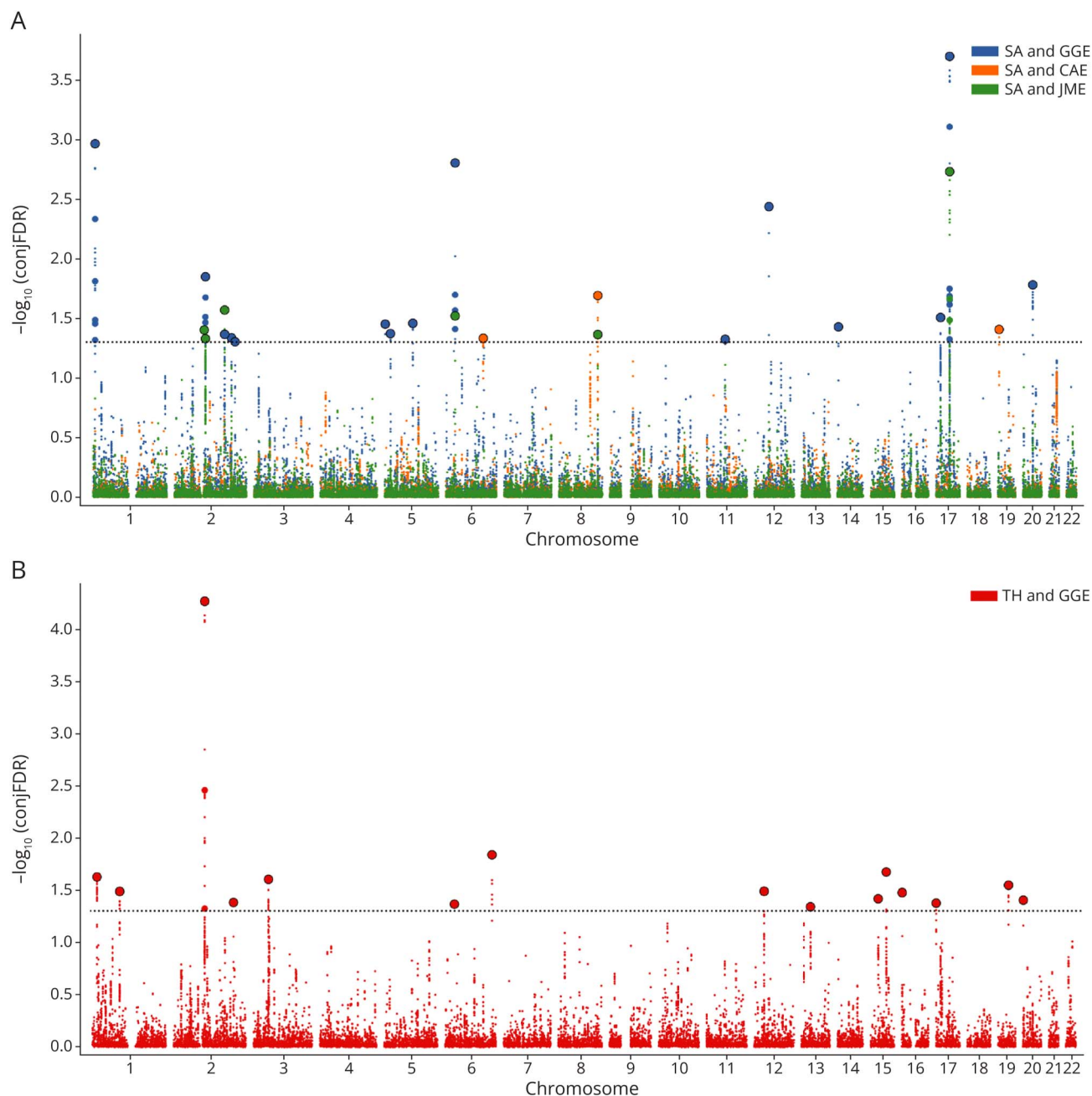
focus on entangling this complex relationship when more well-phenotyped epilepsies and regional cortical GWAS data are available.

The results also emphasize genetic heterogeneity across common epilepsies. Previous studies have reported that focal epilepsies have lower SNP heritability compared with GGEs,[14,18,19] indicating that the latter have strong genetic susceptibility. The low SNP heritability of focal epilepsies also affects the power of the statistical analyses, which was insufficient for both MiXeR and conjFDR analyses despite similar sample sizes as the generalized epilepsies. Similarly, although the GGE subgroup JME has larger SNP heritability estimates ($h^2 = 0.94$, SE = 0.12) than GGE itself ($h^2 = 0.60$, SE = 0.05) (eTable 1), the larger sample size for GGE resulted in more power for the conjFDR analysis. Accordingly, most (82%) of the identified loci shared between epilepsies and cortical morphology associated with GGE. It should be noted that GGE subgroups juvenile absence epilepsy and generalized tonic-clonic seizures had the smallest sample sizes among the phenotypes tested in this study, hence lacked sufficient statistical power in all of our analyses. The results related to these phenotypes such as the LDSC analysis should, therefore, be interpreted with caution.

Among the jointly associated loci, 5 were linked to more than one epilepsy type, indicating consistent effects across the generalized epilepsies. In this study, 7 of the loci associated with GGE, including the locus at the MHC region, have been previously identified in the most recent ILAE GWAS and/or in a previous conjFDR study, supporting the validity of these findings.[14,19] The MHC region consists of a complex LD structure, encompassing numerous genes, with genetic variants associated with adaptive and innate immunity and synaptic maturation during brain development.[46] Hence, our finding is indicative of the involvement of the MHC region in epilepsies and cortical morphology, rather than a particular locus or gene. Furthermore, we found that JME and CAE shared loci with SA but not with TH. SA and TH are influenced by distinct developmental mechanisms, linking SA to gene regulation in neural progenitor cells and TH to adult-specific active regulatory modules, which support the radial unit hypothesis.[13] Given that JME and CAE groups consist of children, our findings may reflect these distinct mechanisms by the number of loci identified with SA and TH.

To provide biological insights into the shared loci between epilepsies and the cortical brain measures, we mapped all lead SNPs in the loci using the OpenTargets resource (eTables 15–18). While the gene-set analyses were underpowered, we note that several of the implicated genes were involved in the mammalian target of rapamycin (mTOR) signaling pathway and transcription regulation. Specifically, 4 of the mapped genes (*ELL2*, *NAB1*, *IRX4*, and *PIAS4*) are involved in regulation of transcription while 3 (*PRKAG1*, *ULK3*, and *YWHAE*) are involved in the mTOR signaling pathway.[47] The mTOR signaling pathway has previously been associated with

(A) Common genetic variants jointly associated with SA and genetic generalized epilepsies (GGE, JME, and CAE) at conjunctional false discovery rate (conjFDR) <0.05. Manhattan plots showing the –log10-transformed conjFDR values for each single nucleotide polymorphism (SNP) on the y-axis and chromosomal positions along the x-axis. The dotted line represents the conjFDR threshold for significant association <0.05. . (B) Common genetic variants jointly associated with TH and GGE at conjFDR <0.05. Manhattan plots showing the –log10-transformed conjFDR values for each SNP on the y-axis and chromosomal positions along the x-axis. The dotted line represents the conjFDR threshold for significant association <0.05. CAE = childhood absence epilepsy; GGE = genetic generalized epilepsies; JME = juvenile myoclonic epilepsy; SA = total cortical surface area; TH = average cortical thickness.

both epilepsies and cortical malformations, where mTOR hyperactivation has been linked to various brain abnormalities and disorders.[48] In addition to genes related to mTOR, which functions as a serine/threonine kinase, there were also other serine/threonine kinase genes (*STK35* and *STK39*) as novel findings among the mapped genes, in line with a recent study reporting overlapping genomic loci between epilepsy and psychiatric disorders.[19]

Serine/threonine kinases are crucial for regulating neuronal activity, including neurotransmitter release and synaptic transmission.[49] Overall, the findings may provide new hypotheses into the shared biology underlying brain formation and epilepsies. However, further functional validation is needed to clarify how and to what extent the implicated genes and genetic variants are involved in epilepsies and brain structure.

Although the conjFDR method cannot identify the underlying causal variant of the SNP associations, because a significant SNP may be in LD with several nearby SNPs, we have highlighted several candidate SNPs that are the most likely causal variants in the loci for follow-up investigations. Another limitation is that, despite excluding participants with a neurologic or psychiatric disorder, we cannot exclude the possibility that participants in the cortical morphology GWAS may develop epilepsy later in life, which may have affected the measures of SA and TH. However, this potential bias cannot explain the findings of mixed effect directions in the shared loci. We also note that the measures of SA and TH may not reflect the whole population, because these measures are taken from the UK Biobank, which is prone to participation bias and involves participants of middle to old age.[50] However, the highly concordant sign concordance results in the independent ENIGMA data set,[13] which was based on a younger population, supports the validity of the findings. Finally, another limitation was using data sets with European ancestry only. While this ensures LD compatibility to avoid bias in conjFDR analyses, it also means that our results may not be generalized to other ancestries, warranting larger GWAS samples based on more diverse populations.

In conclusion, we show that there is a substantial polygenic overlap between genetic generalized epilepsies and SA and TH despite an absence of genetic correlations, providing new insights into their shared genetic architecture, implicating a series of potentially shared molecular pathways. As such, the findings indicate that common genetic variants may contribute to cortical abnormalities in patients with epilepsy.

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Disclosure

O.A. Andreassen has received speaker's honorarium from Lundbeck, Sunovion, Janssen and is a consultant for Cortechs.ai; A.M. Dale is a founder of and holds equity interest in CorTechs Labs and serves on its scientific advisory board. He is also a member of the Scientific Advisory Board of Healthlytix and receives research funding from General Electric Health care (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict-of-interest policies. Remaining authors have no conflicts of interest to declare. Go to Neurology.org/NG for full disclosures.

Publication History

Appendix Authors

Name	Location	Contribution
Naz Karadag, MSc	Institute of Clinical Medicine, NORMENT, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Espen Hagen, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Alexey A. Shadrin, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo; K.G. Jebsen Centre for Neurodevelopmental Disorders, University of Oslo and Oslo University Hospital, Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Dennis van der Meer, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo, Norway; Faculty of Health, School of Mental Health and Neuroscience, Maastricht University, Netherlands	Drafting/revision of the manuscript for content, including medical writing for content
Kevin S. O'Connell, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content
Zillur Rahman, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Gleda Kutrolli, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Nadine Parker, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Appendix *(continued)*

Name	Location	Contribution
Shahram Bahrami, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content
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Erik Taubøll, MD, PhD	Department of Neurology, Oslo University Hospital; Faculty of Medicine, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content
Nils Eiel Steen, MD, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo; Division of Mental Health and Addiction, Oslo University Hospital; Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content
Srdjan Djurovic, PhD	Department of Medical Genetics, Oslo University Hospital; Department of Clinical Science, NORMENT, University of Bergen, Norway	Drafting/revision of the manuscript for content, including medical writing for content
Anders M. Dale, PhD	Department of Cognitive Science; Multimodal Imaging Laboratory; Department of Psychiatry; Department of Neurosciences, University of California, San Diego; Department of Informatics, Center for Bioinformatics, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content
Oleksandr Frei, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo; Department of Informatics, Center for Bioinformatics, University of Oslo, Norway	Drafting/revision of the manuscript for content, including medical writing for content
Ole A. Andreassen, MD, PhD	Institute of Clinical Medicine, NORMENT, University of Oslo; K.G. Jebsen Centre for Neurodevelopmental Disorders, University of Oslo and Oslo University Hospital; Division of Mental Health and Addiction, Oslo University Hospital, Norway	Drafting/revision of the manuscript for content, including medical writing for content
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