ANNUAL REVIEWS

Annual Review of Genomics and Human Genetics

The Genetics of Epilepsy

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Annu. Rev. Genom. Hum. Genet. 2020. 21:205–30

First published as a Review in Advance on April 27, 2020

The *Annual Review of Genomics and Human Genetics* is online at genom.annualreviews.org

https://doi.org/10.1146/annurev-genom-120219-074937

Keywords

epilepsy, genetics, epilepsy genes, genome-wide association study, GWAS, repeat expansions, polygenic risk scores, oligogenic models

Abstract

Epilepsy encompasses a group of heterogeneous brain diseases that affect more than 50 million people worldwide. Epilepsy may have discernible structural, infectious, metabolic, and immune etiologies; however, in most people with epilepsy, no obvious cause is identifiable. Based initially on family studies and later on advances in gene sequencing technologies and computational approaches, as well as the establishment of large collaborative initiatives, we now know that genetics plays a much greater role in epilepsy than was previously appreciated. Here, we review the progress in the field of epilepsy genetics and highlight molecular discoveries in the most important epilepsy groups, including those that have been long considered to have a nongenetic cause. We discuss where the field of epilepsy genetics is moving as it enters a new era in which the genetic architecture of common epilepsies is starting to be unraveled.

1. INTRODUCTION

Epilepsy is a group of brain diseases characterized by an enduring predisposition to generate epileptic seizures (58). Accordingly, seizures constitute the primary symptom of epilepsy. Epileptic seizures can also occur as isolated events not associated with the enduring predisposition, and as such, the occurrence of a seizure may not necessarily imply a diagnosis of epilepsy.

Epilepsy is one of the most common neurological illnesses and can affect individuals of any age, sex, and ethnicity (38). In industrialized countries, up to 10% of people will experience a seizure during their lifetime, and 3–4% will develop epilepsy (68). The lifetime risk of epilepsy is even higher in low- and middle-income countries (54). Epilepsy has adverse effects on social, vocational, physical, and psychological function (61). In the Global Burden of Disease 2010 study, epilepsy ranked as the second-most-burdensome neurological illness in terms of disability-adjusted life years (107).

In 2017, the International League Against Epilepsy (ILAE) revised the classification of the epilepsies, which is now organized on three levels (130) (**Figure 1**). The first level consists of defining the seizure types. Seizures can be broadly categorized into focal seizures (originating within brain networks limited to one hemisphere), generalized seizures (originating at some point within, and rapidly engaging, bilaterally distributed brain networks), and seizures of unknown onset (if there is insufficient information to classify the seizure as focal or generalized) (57). The second level is the diagnosis of the epilepsy type, which comprises four main classes: focal epilepsy, generalized epilepsy, combined focal and generalized epilepsy, and unknown epilepsy. This level includes a new category of combined focal and generalized epilepsy, reflecting the existence of shared mechanisms between the well-established groups of focal epilepsy and generalized epilepsy. The third level is the delineation of the epilepsy syndrome, when a specific syndromic diagnosis can be made. The revised classification emphasizes the importance of establishing the etiology at each of the three levels, due to their implications for clinical management; the etiological categories are structural, genetic, infectious, metabolic, immune, and unknown. The new classification also emphasizes the recognition of comorbidities. Epilepsy is not just seizures; rather, people with epilepsy may have coexistent neurobehavioral and neuropsychiatric symptoms that were previously regarded as a consequence of epilepsy. Now we know that they are, at least in part, a

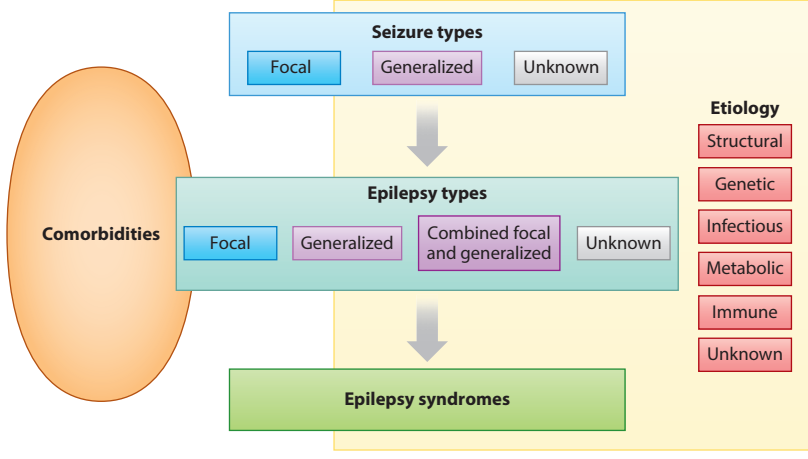

Figure 1

International League Against Epilepsy 2017 classification of the epilepsies. Figure adapted from Reference 130 with permission.

feature of the fundamental disorder, an observation that is now supported by genetic findings (see Section 3).

Classic epidemiological studies have demonstrated that in approximately one-quarter of incident epilepsy cases, there is an evident underlying acquired cause; common causes include stroke, brain tumors, head injuries, brain infections, and degenerative disorders. In the remaining three-quarters of cases, the underlying etiology is unknown (64). In recent years, subtle brain lesions detectable on increasingly sensitive magnetic resonance imaging (MRI), autoimmune causes, and Mendelian epilepsies have been shown to account for a proportion of unsolved cases, yet the underlying etiology remains nonobvious in most people with epilepsy. As detailed in the sections below, the accumulating data driven by recent advances in gene sequencing technology have fueled the hypothesis that genetics plays a major role in these cases. Furthermore, emerging evidence indicates that, even when a major acquired etiology is identified, genetic factors can contribute to the phenotypic expression of certain forms of epilepsy.

2. EPILEPSY VERSUS OTHER DISORDERS: A GENETICS PERSPECTIVE

2.1. Sequencing-Based Gene and Variant Discovery Approaches

Sequencing approaches, such as targeted sequencing, whole-exome sequencing (WES), and whole-genome sequencing (WGS), have been highly successful in epilepsy, detecting causative variants in many patients (as evidenced by their current widespread use in child neurology practice) as well as accelerating novel gene discovery (45). In particular, de novo mutation discovery, facilitated through the powerful parent–child trio design, has resulted in the identification of many additional epilepsy genes, especially in the developmental and epileptic encephalopathies (DEEs) (49).

Sequencing is most commonly applied to lymphocyte-derived DNA to search for pathogenic germline variants. It is also being increasingly applied to other tissues, especially brain specimens, to detect pathogenic somatic variants, which are emerging as playing a significant role in causation (123, 162). Somatic variation is best identified by comparing variation in pathological tissues with putatively unaffected (typically lymphocyte-derived) tissues (162). Somatic mutations causing brain disease can sometimes be found at low abundance outside the brain, detected in buccal cell or lymphocyte-derived DNA or in cell-free DNA from plasma, by applying deep exome sequencing, deep targeted sequencing, or digital droplet PCR (69, 139, 140).

Although cohort-based rare-variant analysis has been a highly successful approach in some forms of epilepsy, such as DEEs (49), the discovery rate with current standard technologies appears to be slowing, and increasingly larger cohorts are now needed to identify novel epilepsy genes in only a few patients (51). Notably, rare-variant burden approaches currently focus almost entirely on coding variants, and methods that allow filtering of the much larger numbers of noncoding variants (there are 100 times more noncoding variants than coding variants) still need to be developed further. These methods require substantial additional external data, such as those generated by the Encyclopedia of DNA Elements (ENCODE) Consortium (91), to identify appropriate regions or variants to examine, ultimately helping to reduce the multiple-testing burden. Several pathogenic intronic and other noncoding mutations have been identified in patients with epilepsy, as detailed below.

2.2. Genome-Wide Association Studies

In 2018, the ILAE Consortium on Complex Epilepsies published the largest genome-wide association study (GWAS) to date in epilepsy, involving 15,212 cases and 29,677 controls (73),

Supplemental Material >

although this is a modest size compared with studies of schizophrenia (~37,000 cases) (134). It revealed 16 genome-wide significant loci for epilepsy, of which 11 were novel (73). Some of the genes corresponding to these loci, such as *SCN1A*, *SCN2A*, and *PNPO*, overlapped with established epilepsy genes identified through traditional linkage and sequencing analysis (**Supplemental Table 1**). Importantly, this GWAS yielded enough loci to permit a whole raft of additional post-GWAS analyses, utilizing methods such as Mendelian randomization (46), linkage disequilibrium score regression–type approaches (142), multitrait analysis of GWAS (MTAG) (154), and transcriptome-wide association studies (157).

A further GWAS by the ILAE Consortium on Complex Epilepsies is currently underway, with results expected by 2021. This analysis will double the case sample size and should reveal further epilepsy genetic risk loci.

2.3. Current Understanding of the Genetic Architecture of Epilepsies

Our current understanding is that the epilepsies comprise a large number of rare Mendelian subtypes, with the more common forms having a likely oligo- or polygenic architecture with both common- and rare-variant contributions (45). Even in acquired epilepsies, such as those resulting from a severe head injury or stroke, genetic factors play a role, as shown by family history data (20, 53), although the actual variants have not been identified.

The large number of identifiable Mendelian subtypes and the number of genes already known are what set epilepsy apart from other complex disorders, such as type 2 diabetes, schizophrenia, and age-related macular degeneration. Epilepsy's special genetic architecture can be illustrated by comparing or benchmarking the current knowledge of epilepsy genetics for both common- and rare-variant contributions to that of other neurological conditions as well as common nonneurological disorders (**Figure 2**). These comparisons should be interpreted with caution, since the disorders have been investigated with different sample sizes, which affects the number of discoveries and the accuracy of effect sizes. Our common-variant analysis (**Figure 2*a***) focuses on the distribution of the effect sizes of the most strongly associated single-nucleotide polymorphisms (SNPs) per genome-wide significant GWAS, rather than the number of signals discovered for each disease, as the latter will be larger for diseases studied with larger sample sizes.

It is recognized that some of the genetic contributions to complex diseases are currently impossible to investigate, likely forming part of the genetic missing heritability (164). The inability to investigate these contributions is due to several factors, including (*a*) the lack of appropriate analytical methods, (*b*) the hypothesized large increases in sample size necessary to be able to accommodate the anticipated increased multiple-testing burden for these analyses, and (*c*) the multiomics approach (and its currently prohibitive cost) that is likely required to generate all the data needed to interrogate methylation, histone modifications, transcriptomes, and so on. Hence, the genetic understanding of complex diseases such as epilepsy is still limited, with only a fraction of the phenotypic variation due to genetic factors currently captured by existing approaches, such as GWAS and sequencing-based analysis, in their current forms.

3. THE GENETICS OF DIFFERENT EPILEPSIES

3.1. Chromosomal, Genomic, and Syndromic Disorders

Epilepsy is listed in hundreds of entries in the Online Mendelian Inheritance in Man (OMIM) database (**Figure 2*b***), and in many examples, genes harboring pathogenic variants have been identified. However, there is a divergence between clinical geneticists and epileptologists in the diagnostic approach to disorders that include epilepsy or seizures.

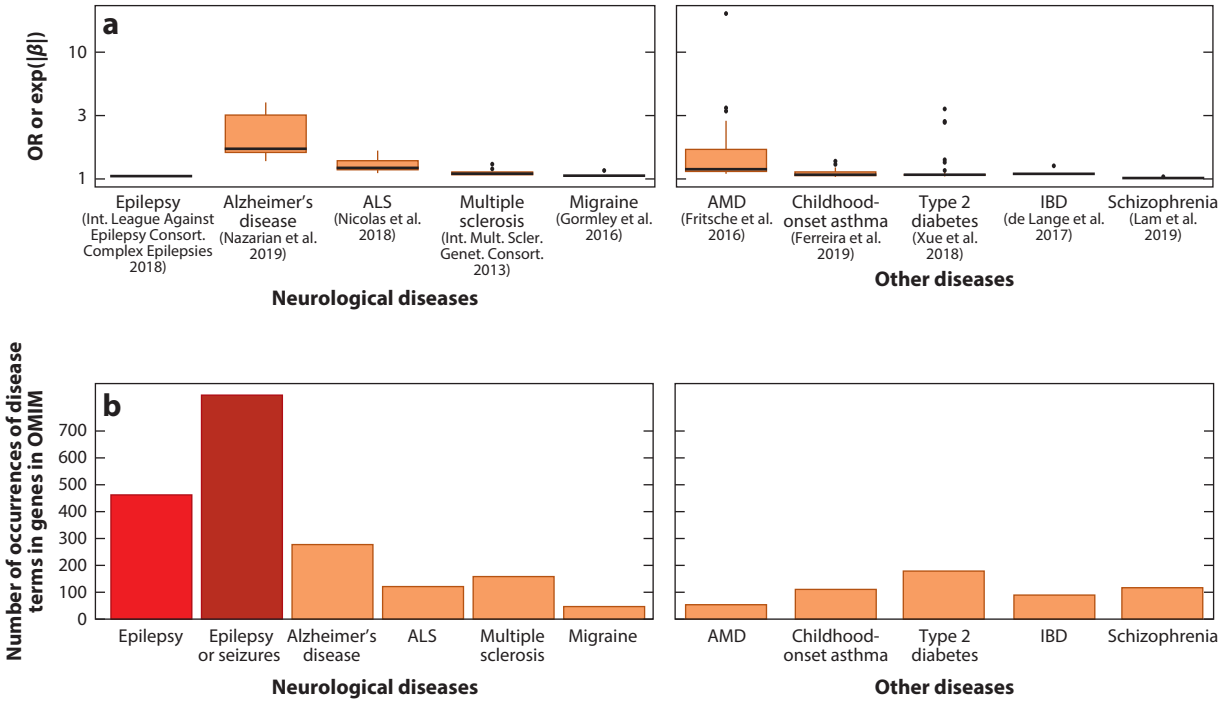

Figure 2

Estimates of the contributions of (*a*) common and (*b*) rare variants in epilepsy versus other disorders. (*a*) ORs displayed as box plots by disease, along with the median and interquartile ranges on a $\log_{10}$ scale for the SNP most strongly associated with specific disease loci in a recently published GWAS for that disease. The left subpanel shows a sample of neurological diseases, including epilepsy (*red box plot*), and the right subpanel shows nonneurological diseases. Higher OR values indicate a greater SNP effect size. For logistic regression models, we used the conversion $\text{OR} = \exp(|\beta|)$, where β is the effect size of the SNP. We converted *Z*-scores from meta-analyses to β using METAL (159) output with $\beta = Z\sqrt{\text{SE}(\beta)}$. Only loci with a *p* value of less than 5×10^{-8} are displayed. Data are from the NHGRI-EBI GWAS Catalog (accessed November 20, 2019). (*b*) Number of hits of relevant disease terms in OMIM for neurological diseases (*left subpanel*), including epilepsy (*red*) and seizures/epilepsy (*dark red*), and nonneurological diseases (*right subpanel*). Data are from the OMIM database (accessed on October 10, 2019). Abbreviations: ALS, amyotrophic lateral sclerosis; AMD, age-related macular degeneration; EBI, European Bioinformatics Institute; GWAS, genome-wide association study; IBD, inflammatory bowel disease; NHGRI, National Human Genome Research Institute; OMIM, Online Mendelian Inheritance in Man; OR, odds ratio; SNP, single-nucleotide polymorphism.

To the frustration of many epileptologists, clinical genetic descriptions of disorders with seizures are sometimes communicated as little more than that. By contrast, the classification of seizure disorders and of epilepsies in individual subjects has become highly sophisticated and evidence based (57, 130). Why is there still a divergence in terminology and approach between the two disciplines? Some of it is rooted in the different clinical approaches and training between disciplines, but much has a basis in biological variability across subjects between and even within families when they have the same genetic abnormality.

In some familial epilepsies, affected individuals may have similar or identical seizure types and epilepsy phenotypes, but this is not always the case. For example, in benign neonatal familial epilepsy, the pattern of repetitive focal seizures beginning at around 2–5 days of age is often reproducible, recognized by families and physicians in cases with an affected older sibling or parent (63). Similarly, adolescents and adults with autosomal dominant epilepsy with auditory features due to pathogenic variants in *LGI1* typically have a relatively similar phenotype of focal seizures, usually

preceded by auditory or other manifestations resulting from involvement of the temporo-occipital region (102). However, there are other familial epilepsies, for example, those associated with pathogenic *DEPDC5* variants, where heterogeneous patterns of focal epilepsy are observed (40). In the disorder of genetic epilepsy with febrile seizures plus (GEFS+), which is sometimes due to pathogenic variants in sodium-channel genes, a spectrum of epilepsies is seen, from benign self-limited febrile seizures to the severe disorder of Dravet syndrome (165). This heterogeneity is not yet well explained; mechanisms such as modifier genes have been postulated but not yet definitively shown.

Similarly, in syndromic epilepsies, there are rather few genomic disorders where the seizure pattern is relatively uniform and recognizable. Ring chromosome 20 syndrome is associated with frequent daytime episodes of confusion typically lasting 10–20 min (prolonged focal impaired-awareness seizures), with or without tonic attacks at night, and a characteristic ictal electroencephalogram (EEG) pattern consisting of high-voltage rhythmic slow activity (29). Angelman syndrome is characterized by seizure onset around age 1–3 years and a generalized epilepsy pattern of atypical absences, atonic seizures, myoclonic seizures, and episodes of myoclonic status epilepticus with an abnormal EEG showing frontally predominant, high-voltage, 2–3-Hz activity with spikes and sharp waves, often facilitated by eye closure (117).

The general rule is, however, that genomic disorders have quite variable associations with epilepsy in terms of both its presence and the seizure types and epilepsy syndromes. For example, in trisomy 21, there was debate as to whether seizures were part of the phenotype; it is now well established that they are, but the seizures can vary from severe infantile spasms that typically present around the middle of the first year of life to a relatively mild generalized form of epilepsy with drop attacks beginning in middle life, and there are a wide variety of other patterns in between (124). The reason for this diversity is not known.

Similarly, genetic disorders caused by sequence variation may exhibit marked variation among and within families. In tuberous sclerosis complex, which is due to dominant pathogenic variants in *TSC1* or *TSC2*, seizures are a common but not invariable manifestation. These disorders can vary from a severe infantile epilepsy, with tuberous sclerosis complex being one of the important causes of West syndrome with infantile spasms, to a mild, later-onset focal epilepsy (28). Here, we have at least a partial explanation in that the localization of the seizure foci (and perhaps their severity) is determined by the location and number of tubers that histologically are type IIB cortical dysplasias, which are known to be highly epileptogenic abnormalities (28). Another example of marked heterogeneity are epilepsies associated with the enlarging spectrum of phenotypes associated with pathogenic variants in *TBC1D24*. From a genetic syndrome viewpoint, this gene has been associated with deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures (DOORS) syndrome, with seizures being an inconstant feature (14). From an epilepsy viewpoint, however, *TBC1D24* has also been described as a cause of familial myoclonic epilepsy in infancy (a familial syndrome of focal epilepsy with cortical and cerebellar abnormalities) and as a de novo dominant cause of the severe epilepsy syndrome of migrating focal seizures of infancy (which typically does not include deafness, nail, or bone abnormalities) (6). One might posit that pathogenic variants in different parts of the gene are responsible for this variation, but this hypothesis remains to be investigated.

Thus, in terms of understanding the genotype–phenotype correlation in epilepsies, there is a paradox. The epileptologist recognizes epilepsy syndromes, which are characterized by an aggregation of seizure types, EEG patterns, age of onset, and so on. These syndromes are often genetic in origin and of considerable value in determining treatment and prognosis and offering counseling, although the molecular basis may not yet be known or (if it is known) is often heterogeneous. By contrast, the clinical geneticist may identify syndromic epilepsies, where seizures are thought

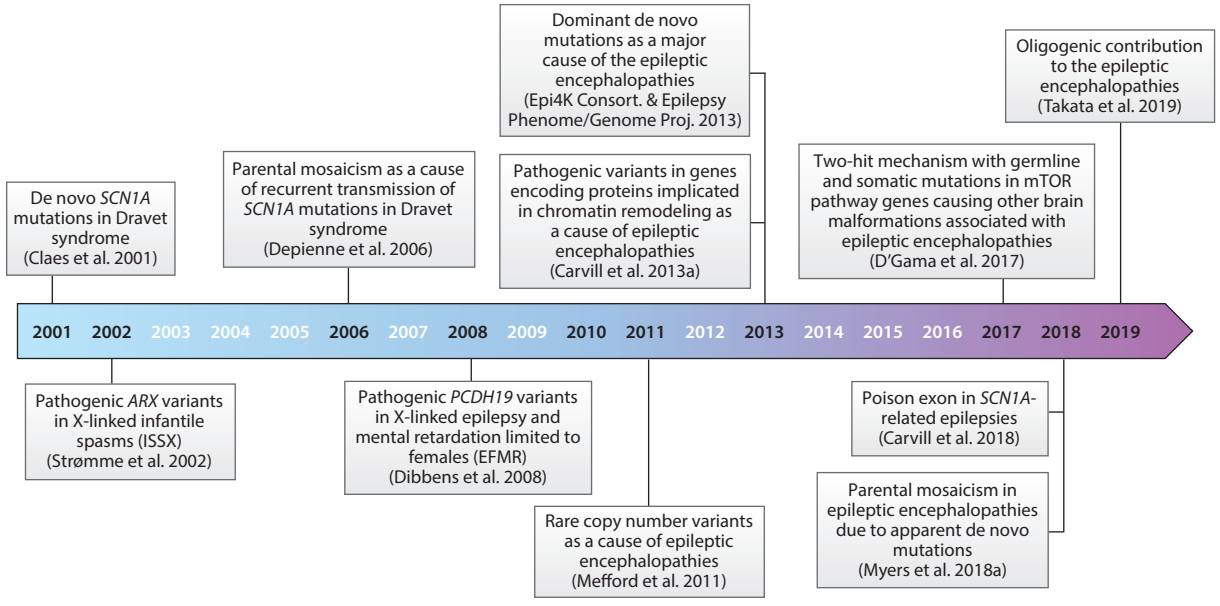

Figure 3

Time line of major molecular discoveries in the epileptic encephalopathies.

of as being part of a multisystem abnormality, often underpinned by a genomic disorder, and here the epileptology is usually highly variable.

3.2. Developmental and Epileptic Encephalopathies

The impact of genetic discoveries in epilepsy has been greatest in the group of disorders now known as DEEs (**Figure 3**). These disorders are individually rare but overall occur in 1 in 2,000 live births per year (70). Due to their severity, they account for a considerable portion of the burden of epilepsy, and for patients and their families, that burden is lifelong (70).

It has long been recognized that, in infants and children, epilepsy (often severe and intractable) occurs together with developmental abnormalities and intellectual disability. It was rare, however, for a specific diagnosis to be made, and often the diagnosis was "epilepsy and intellectual disability." The cause was often misattributed to pre- or perinatal factors and sometimes to postnatal events, such as vaccination. The landscape of these disorders has changed considerably from one of absence of diagnosis and therapeutic nihilism to an exciting area, comprising specific diagnoses and counseling, neurobiological insights, and the promise of precision therapies.

3.2.1. Definitions. The epileptic encephalopathies are defined as disorders where "the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone (e.g., cortical malformation), and. . .can worsen over time" (9, p. 682). An important inference is that better treatment of the epilepsy may improve cognition. Developmental encephalopathies imply that seizures per se are not the key driver of the impairment. These processes overlap and may occur in the same patient (130).

DEEs can be due to acquired factors (e.g., perinatal strokes, infections, or trauma) and well-known and diagnosable genetic disorders, such as tuberous sclerosis complex (99). There are a

large number of cases with no obvious extraneous cause or family history and in which investigations (including neuroimaging) show no specific abnormality. It is now clear that the majority of these cases are due to a heterogeneous group of genetic disorders and that many are now diagnosable. The proportion of currently diagnosable cases is difficult to accurately quantitate—selection bias weighs heavily on published series, as does the intensity of investigation, be it in a clinical or research setting. Overall, currently a figure of 40% would not be regarded as overly optimistic (66), and some selected series report in excess of 80% (137). In addition to cases with obvious lesions, cortical malformations, which may be subtle on MRI, can present with a DEE phenotype and often have a discoverable genetic basis. When focal, these cases include mTORopathies, particularly with pathogenic variants in *DEPDC5* but also in *NPRL2* and *NPRL3* (Section 3.4). Recognition is important because early epilepsy surgery may reverse the encephalopathy.

Gene discovery has also led to a reconsideration of phenotypic features. These features are often complex in terms of seizure patterns, clinical comorbidities, and EEG features, but the gene discoveries have allowed clinical researchers to focus on genetically homogeneous groups of subjects and define the phenotypic spectrum. We do not attempt an exhaustive listing of all the disorders and genetic findings, as they continue to be described on an almost weekly basis; rather, we provide a current overview of this evolving field.

3.2.2. Dravet syndrome. Dravet syndrome is the archetypal condition among the DEEs. The history of discovery underlies many of the principles that we now understand in this broad group. Initially described by Charlotte Dravet in 1978, the clinical pattern is complex and was not widely recognized outside Europe until many years later (44). Children are initially normal and around 6 months of age begin having seizures, often accompanied by fever. The initial seizures can be quite prolonged or even status epilepticus, and classically hemiclonic seizures with fever occur. Seizures continue episodically in the first year of life; in the second year, developmental slowing may become apparent and other seizure types may appear, including myoclonic seizures, tonic–clonic seizures, and focal seizures. Sensitivity to fever persists, and seizures continue throughout life, with most patients having intractable seizures. Surprisingly, the EEG in the first two years of life may be normal, but multifocal abnormalities appear later. The MRI is normal apart from atrophy in some cases and (rarely) hippocampal damage (44). Up to one-fifth of children with Dravet syndrome will die by the age of 20, mostly of sudden unexpected death in epilepsy (22). Intellectual impairment is typically moderate to severe; rare patients will be able to function independently (44).

The cause of Dravet syndrome long remained a mystery, but in 2001 de novo pathogenic variants in the *SCN1A* gene were discovered (21), and this observation has been repeatedly confirmed (99). Approximately 90% of patients with clinical Dravet syndrome have pathogenic *SCN1A* variants (21, 94); approximately half of these variants predict protein truncation, and half are splice-site or missense variants (94). The cause of the remaining 10% has been a source of much interest. A few patients have large deletions in *SCN1A* and adjacent regions (94); recently, poison exons have been recognized in a small number of cases with otherwise typical Dravet syndrome (15). A small number of pathogenic variants in some other genes (e.g., *PCDH19*, *GABRA1*, *GABRG2*, *HCN1*, or *KCNA2*) have phenotypes that are generally regarded as falling within the Dravet spectrum (143). Finally, recessive mutations in the auxiliary sodium-channel subunit gene *SCN1B* have been described in a few cases, but a small proportion of subjects with Dravet syndrome continue to defy molecular explanation (143).

3.2.3. Other major electroclinical syndromes. The DEE group includes several other defined electroclinical syndromes; the close relationship of phenotype to genotype seen in Dravet

syndrome is not as clear, but certain genes stand out as critical. These syndromes are best understood in terms of their age-dependent expression, although many patients with DEEs are not classifiable into one of these specific disorders.

Ohtahara syndrome, also known as early-onset infantile encephalopathy, presents in the first few weeks of life with severe tonic seizures and a characteristic EEG with burst suppression. The infants are severely impaired. The disorder has heterogeneous causes, but in terms of genetic etiology, pathogenic variants in *STXBP1*, *KCNQ2*, and *SCN2A* are most important (99).

Epilepsy in infancy with migrating focal seizures is another disorder that was described many years ago but not widely recognized until genetic discoveries emerged. Infants in the first few months of life have focal seizures that originate in various parts of the brain and spread from one spot to another in a single seizure. The genetic architecture of this disorder has recently been exhaustively examined; the most commonly associated genes are *KCNT1* and *SCN2A*, but a large number of other genes contribute to a small proportion of cases (13, 99).

West syndrome, described more than 100 years ago by a doctor in his own son, is a classical syndrome presenting with infantile spasms around the age of 6 months in association with intellectual disability and a characteristic EEG pattern known as hypsarrhythmia. It can result from a variety of causes—both genetic and acquired—and one of the long-recognized common causes is tuberous sclerosis complex, which in itself has many presentations in terms of the associated epileptic syndrome. More recently, West syndrome has been shown to be potentially caused by a wide variety of other genes, including *ARX*, *CDKL5*, *SPTAN1*, and *STXBP1* (99).

Lennox–Gastaut syndrome is a relatively common encephalopathy presenting later in life, although it may evolve from West syndrome. The pattern is of tonic and atonic seizures associated with slow spike-and-wave discharges on EEG. It may be due to acquired lesions, including focal abnormalities; it has typically been regarded as a generalized encephalopathy but is now conceptualized as a disorder causing a secondary network epilepsy. Genes associated with Lennox–Gastaut syndrome of nonacquired cause include *ALG13*, *CACNA1A*, *CDKL5*, *CHD2*, *DNM1*, *GABRB3*, *HNPRNU*, *SCN2A*, *SCN8A*, and *STXBP1* (99). Further details on other, less common DEEs have been reviewed by McTague et al. (99).

It is notable that these syndromes are clinically recognizable and present in an age-dependent fashion; they are viewed as age-dependent responses of the developing brain to a variety of insults, which explains why the causes can be so heterogeneous. While recognition of these syndromes may lead to a targeted search for variants in a particular gene—notably sodium-channel variants in Dravet syndrome—in most cases of children with a DEE and no specific MRI abnormality, the most practical approach is with a gene panel or a hypothesis-free genome-wide study, ideally as a trio, as most of these disorders are due to de novo mutations (49). It is important to consider other modes of inheritance. Recessive disorders, long recognized in aminoacidopathies and related inborn errors in metabolism, can cause DEEs, but other genes also cause DEEs with a recessive model. This needs consideration in both consanguineous and outbred populations (110, 116).

X-linked disorders are also important, and the remarkable phenomenon of *PCH19*-related epilepsy deserves special mention. Here, the gene on the X chromosome causes disease only in girls, males being healthy transmitting carriers. Caveats include the facts that several mosaic males have been described and that there is some evidence that the transmitting males have subtle behavioral characteristics. The mechanism of this reverse X-linked transmission appears to be cellular interference, where *PCDH19*, which is involved in cellular communication, does not lead to a phenotype in hemizygous males (or, presumably, homozygous mutant females) but does result in significant abnormalities when the patient is heterozygous, as in affected females.

Finally, in addition to the major effect of de novo variants, in some DEE cases there is evidence for concomitant pathogenic variants, suggesting an oligogenic contribution in a subset of these disorders (149).

3.3. Genetic Generalized Epilepsies

Genetic generalized epilepsies (GGEs) account for 15–20% of all epilepsies (77). They are typically characterized by absence, myoclonic, and generalized tonic–clonic seizures; normal intellect; generalized spike-wave discharges at >2.5 Hz on the EEG; and unremarkable neuroimaging (105). GGEs were formerly referred to as idiopathic generalized epilepsies, but the term idiopathic was replaced by genetic in the new ILAE classification of the epilepsies, in recognition of the important genetic contributions to this epilepsy group (130). However, the designation idiopathic generalized epilepsies can still be used when referring collectively to four specific syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized tonic–clonic seizures alone (formerly referred to as generalized tonic–clonic seizures on awakening) (130).

3.3.1. Genetic contributions to genetic generalized epilepsies: evidence from epidemiological and twin studies. Different lines of evidence support the revised terminology of GGEs. Population-based familial aggregation studies indicate that the risk of developing epilepsy among first-degree relatives of probands with GGE is up to six times that of the general population (118). Several twin studies have shown substantially higher concordances for GGE in monozygotic twins than in dizygotic twins (26, 155). In a study of 1,323 twin pairs with seizures ascertained from population-based twin registries in Denmark, Norway, and the United States, concordance estimates were higher in monozygotic twins than in dizygotic twins for the entire group of the GGEs (0.66 versus 0.10, $p < 0.0001$), as well as for the four main generalized epilepsy syndromes: childhood absence epilepsy (0.55 versus 0.10, $p < 0.01$), juvenile absence epilepsy (0.89 versus 0.13, $p < 0.01$), juvenile myoclonic epilepsy (0.53 versus 0.08, $p < 0.0001$), and generalized tonic–clonic seizures alone (0.40 versus 0, $p < 0.05$) (26). Furthermore, families with multiple members with GGEs have long been observed. Of 303 multiplex families with common epilepsies recruited through the international Epi4K Consortium, 117 (38.6%) exclusively segregated GGEs (48). Among these pedigrees, absence epilepsies clustered within families independently of juvenile myoclonic epilepsy, and, interestingly, significantly more females were affected than males.

3.3.2. Molecular genetics of genetic generalized epilepsies. The genetic architecture of the GGEs has long been an unsolved mystery. The observations that (*a*) siblings of probands with GGE have an approximately 8% risk of developing epilepsy (118), which is considerably lower than the risk expected for a recessive (25%) or dominant (50%) inherited trait (105), and (*b*) most patients have no apparent immediate family history suggest a largely polygenic pattern of inheritance. However, some cases do display Mendelian inheritance. Early work found that a missense variant in *GABRG2*, encoding the γ-aminobutyric acid ($GABA_A$) receptor γ2 subunit, caused childhood absence epilepsy and febrile seizures in a large Australian family (158). Subsequently, a pathogenic missense variant in another $GABA_A$ receptor gene, *GABRA1*, encoding the α1 subunit, was identified in a large French Canadian pedigree with an autosomal dominant form of juvenile myoclonic epilepsy (27). Although pathogenic variants in these two genes were subsequently identified in other affected individuals (92), they are a rare cause of monogenic GGEs. More prevalent in this group are pathogenic variants in *SLC2A1*, encoding glucose transporter 1 (GLUT1). Variants in this gene were identified initially in a severe infantile metabolic encephalopathy (36,

135) and later in families with milder phenotypes, comprising epilepsy with prominent absence seizures, paroxysmal exertional dyskinesia, and often normal intellect (147). In paroxysmal exertional dyskinesia, prolonged exercise leads to dystonia or chorea, limited largely to the limbs (147). Pathogenic variants in *SLC2A1* were later found to account for approximately 10% of early-onset absence epilepsies (characterized by absence seizures beginning before the age of 4) (2, 148) and approximately 1% of typical GGEs (3). Importantly, detecting these variants can lead to improved patient management (121). GLUT1 is a key transporter required for glucose penetration across the blood–brain barrier. Glucose is the prime source of energy for the brain, and *SCL2A1* mutations resulting in GLUT1 deficiency lead to neuronal dysfunction due to impaired access of glucose to cerebral tissue. Patients with GLUT1 deficiency respond well to the ketogenic diet, because ketones provide an alternative source of energy for the brain, bypassing the metabolic defect and ultimately leading to improved seizure control and, in some cases, intellectual abilities (121).

The search for additional Mendelian causes of GGE continues. A recent study suggested that heterozygous variants in the *ICK* gene, encoding intestinal-cell kinase, can cause juvenile myoclonic epilepsy, and detected *ICK* variants were deemed to be pathogenic in 22 of 310 cases (7%) (4). However, a subsequent multicenter analysis of WES data from 1,149 individuals with GGEs and 5,911 ethnically matched controls failed to find any evidence of an enrichment of rare *ICK* variants in GGE or juvenile myoclonic epilepsy (86). Specifically, no single nonsynonymous variant in *ICK* was identified in 357 cases with juvenile myoclonic epilepsy at a minor allele frequency of 0.1% or less. The lack of replication of the original findings in this cohort argues against a disease-causing potential of *ICK* variants in juvenile myoclonic epilepsy.

Three recent WES case–control studies have shed light on the burden of rare variants in the GGEs (50, 51, 97). The first, performed by the Epi4K Consortium and Epilepsy Phenome/Genome Project, found an excess of ultrarare deleterious variants in known dominant epilepsy genes, including epileptic encephalopathy genes, among 640 individuals with GGE and a family history of epilepsy, although no individual gene achieved statistical significance (50). The enrichment of epileptic encephalopathy genes in the GGE cohort was unexpected; GGEs and epileptic encephalopathies were traditionally viewed as distinct groups. That this view needs modification is reinforced by family studies where genes typically associated with epileptic encephalopathies (often through de novo variants) segregate in families with milder epilepsies, including GGEs (23, 136).

The second study, conducted within the framework of the EPICURE, EuroEPINOMICS CoGIE, and EpiPGX Consortia, showed replicable enrichment of rare missense variants in genes encoding $GABA_A$ receptor subunits in three independent cohorts of individuals with GGE, which collectively comprised 1,092 cases (97). The third study, by the Epi25 Collaborative, refined the findings from the two prior investigations using a larger cohort, demonstrating excess ultrarare deleterious variation in constrained genes, known dominant epilepsy genes (including epileptic encephalopathy genes), and genes associated with specific epilepsy targets among 3,108 individuals with GGE (51). In line with the prior study (97), an enrichment in ultrarare missense variants in $GABA_A$ receptor genes was found (51). Although no gene reached statistical significance, lead associations included highly constrained genes or genes encoding ion channels, such as *CACNA1G*, *EEF1A2*, and *GABRG2*.

Research in the past decade has also highlighted the role of copy number variants as risk factors for epilepsy, including GGEs (152). Three recurrent deletions—two on chromosome 15 (15q13.3 and 15q11.2) and one on chromosome 16 (16p13.11)—are particularly relevant to the GGEs, with approximately 3% of patients carrying at least one of these deletions (34, 65, 100, 106). The 15q13.3 microdeletion, which encompasses seven genes, including the α7

nicotinic receptor subunit gene (*CHRNA7*), confers the greatest risk for GGE (odds ratio 68.2, 95% confidence interval 28.5–181.2) (41). The three deletions are also established risk factors for different development disorders, including intellectual disability, autism spectrum disorders, and schizophrenia (106). It is not unusual for individuals carrying these deletions to have multiple diagnoses. A case–control study found that the frequency of the three deletions among individuals with a GGE-like phenotype and concomitant intellectual disability was more than three times that of individuals with GGE alone (106).

Several GWASs have evaluated the contributions of common variants to the risk of epilepsy, including GGEs, but early efforts were hampered by small sample sizes and insufficient power. A two-stage GWAS that included 3,020 individuals with GGE and 3,954 controls of European ancestry suggested common risk alleles at 2p16.1 and 17q21.32 and reported suggestive evidence for an association with GGE at the *SCN1A* locus (52). Significant associations were also reported at 1q43 for juvenile myoclonic epilepsy and at 2q22.3 for absence epilepsies (52). In 2011, the ILAE launched the Consortium on Complex Epilepsies to apply meta-analytic approaches to GWASs in epilepsy. The first such meta-analysis was published in 2014 and included 8,696 cases with epilepsy and 26,157 controls (72); in the subgroup with GGE ($n = 2,606$), a genome-wide significant association was found at 2p16.1 [as in the previously described GWAS, which was also included in the meta-analysis (52)], implicating *VRK2* or *FANCL* (72). A second, expanded analysis was published in 2018, comprising 15,212 cases with epilepsy and 29,677 controls. In the subgroup with GGE ($n = 3,769$), genome-wide significant associations were found in 11 loci, 7 of which were novel (73) (**Supplemental Table 1**). This was a welcome advance in this highly heritable group of epilepsies where genetic analyses had yielded only modest findings to date. The implicated genes involved ion-channel subunits, transcription factors, and a vitamin B_6 metabolism enzyme. Notably, several of the most plausible candidate genes within these loci overlapped with known targets of antiepileptic drugs or established monogenic epilepsy genes (73) (**Supplemental Table 1**). Furthermore, a partitioned heritability analysis pointed to the dorsolateral prefrontal cortex as a key structure, which is congruent with many orthogonal investigations of GGEs. Finally, for syndromes within the GGEs, significant associations have been found for juvenile myoclonic epilepsy at a novel locus and for childhood absence epilepsy at two loci that had previously been associated with generalized epilepsy (52) (**Supplemental Table 1**).

Supplemental Material >

3.4. Focal Epilepsies

Focal epilepsies account for 60% of all epilepsies and have traditionally been regarded as nongenetic disorders (119). This (mis)perception is related to the common observation that epilepsies resulting from an antecedent central nervous system insult (such as a head injury, stroke, brain infection, or tumor) are focal. However, accruing evidence indicates that there are important genetic contributions to the focal epilepsies (119).

3.4.1. Genetic contributions to focal epilepsies: evidence from epidemiological, twin, and clinical studies. Population-based epidemiological studies have found that the risk of seizures or epilepsy among first-degree relatives of probands with focal epilepsy is two to three times that of the general population (119). The familial risk varies according to the underlying etiology. It is increased among first-degree relatives of probands with focal epilepsy of unknown cause (more than twofold) or prenatal/developmental cause (almost fivefold) but not among first-degree relatives of probands with focal epilepsy of postnatal cause (118). Yet genetic influences may also play a role in this last group. In a Danish population-based study that included more than 1.6 million people, a positive family history of epilepsy carried more than a 10-fold-increased risk

of developing epilepsy following a severe head trauma (20). Furthermore, although affected first-degree relatives of probands with focal epilepsy are also likely to have focal epilepsy, the risk of developing focal epilepsy is similar among relatives of probands with either focal epilepsy or generalized epilepsy (i.e., increased ~2.5-fold) (118), suggesting coexisting shared genetic influences.

Several twin studies have found higher concordances for focal epilepsy in monozygotic twins (0.21–0.40) than in dizygotic twins (0.03–0.12) (11, 25, 155). Concordances vary according to the underlying etiology and the epilepsy syndrome. In an Australian study of 418 twin pairs with confirmed seizures (155), there were higher concordance estimates in monozygotic twins than in dizygotic twins for temporal lobe epilepsy of unknown cause (nonlesional temporal lobe epilepsy) (0.82 versus 0, $p = 0.003$). Concordances did not differ between the two sets of twins for focal epilepsies of structural or metabolic cause.

Several familial focal epilepsy syndromes have been described, each with defining characteristics (**Supplemental Table 2**). Notable syndromes include autosomal dominant sleep-related hypermotor epilepsy (formerly referred to as autosomal dominant nocturnal frontal lobe epilepsy) (153), which is characterized by clusters of brief focal motor seizures with hyperkinetic or tonic features that can be misdiagnosed as parasomnias, psychiatric disorders, or normal sleep phenomena (131); familial mesial temporal lobe epilepsy, which accounts for approximately 20% of new diagnoses of nonlesional mesial temporal lobe epilepsy but is typically unrecognized without direct questioning of patients' relatives due to its mild seizures with prominent déjà vu (12, 120); autosomal dominant epilepsy with auditory features, consisting of focal seizures with auditory hallucinations/illusions or receptive aphasia (114); and familial focal epilepsy with variable foci, in which different members of the same family exhibit a different brain region of seizure onset (i.e., frontal, temporal, parietal, or occipital) (133).

Supplemental Material >

3.4.2. Gene discoveries in focal epilepsies. Remarkably, the first epilepsy gene to be discovered was in focal epilepsy; a missense variant in *CHRNA4*, encoding the neuronal nicotinic acetylcholine receptor α4 subunit, was found to cause autosomal dominant sleep-related hypermotor epilepsy in a large Australian pedigree in the mid-1990s (144). This finding paved the way for a pioneering era of gene discoveries (mainly ion-channel genes) in Mendelian epilepsies. These discoveries included several focal epilepsy genes, such as the voltage-gated potassium genes *KCNQ2* and *KCNQ3*, involved in self-limited familial neonatal epilepsy; the voltage-gated sodium-channel α2 subunit gene *SCN2A*, associated with self-limited familial neonatal-infantile epilepsy; and *LGI*, encoding a neuronal secreted protein, which is implicated in autosomal dominant epilepsy with auditory features. These early discoveries did not lead to a cascade of discoveries in focal epilepsies. Rather, a relatively dormant period followed that was marred by negative candidate gene studies and claims of having identified putative focal epilepsy genes that were not able to be replicated (18).

The introduction of next-generation sequencing led to a new wave of epilepsy gene discoveries, rekindling interest in the molecular genetics of focal epilepsies. Genes encoding the subunits of the GATOR1 complex (*DEPDC5*, *NPRL2*, and *NPRL3*), a negative modulator of the mTOR signaling pathway, emerged as having a major role in this epilepsy group (5, 8). Germline pathogenic variants in *DEPDC5* were detected in 10 of 13 pedigrees with familial focal epilepsy with variable foci (40, 75) and in 10 of 82 smaller families with nonlesional focal epilepsy (40). *DEPDC5* was subsequently found to be implicated in other focal epilepsies, including autosomal dominant sleep-related hypermotor epilepsy (122), rare examples of self-limited epilepsy with centrotemporal spikes (80), and focal epilepsy associated with malformations of cortical development (132). Pathogenic variants in *NPRL2* and *NPRL3* were identified in familial and sporadic focal epilepsies, with or without brain malformations (128).

Other major focal epilepsy gene discoveries have occurred following the advent of next-generation sequencing. *KCNT1*, encoding a sodium-gated potassium-channel subunit, has been associated with epilepsy in infancy with migrating focal seizures, severe autosomal dominant sleep-related hypermotor epilepsy, and other nonlesional and lesional focal epilepsies (7, 67, 129). *GRIN2A*, encoding the *N*-methyl-D-aspartate receptor (NMDAR) subunit GluN2A, was implicated in the epilepsy–aphasia spectrum, a phenotypic continuum ranging from normal or near-normal development with mild focal epilepsy and speech delay/apraxia to severe DEEs (17, 85, 87). The milder phenotypes appear to stem from missense variants within amino-terminal or ligand-binding domains or null variants causing NMDAR loss of function, whereas the severe phenotypes appear to arise from missense variants in the transmembrane and linker domains that result predominantly in NMDAR gain of function (145). *RELN* and, most recently, *MICAL-1* have been implicated in some families with autosomal dominant epilepsy with auditory features negative for *LGI1* pathogenic variants (32, 33), and these findings await replication.

Two recent large international collaborations demonstrated that ultrarare variation in genes associated with rare, often severe forms of epilepsy also contribute to common epilepsies (50, 51). In a study by the Epi4K Consortium and Epilepsy Phenome/Genome Project that included 5,704 individuals with exome sequencing data, excess ultrarare deleterious variation in known epilepsy genes was found in individuals with nonlesional focal epilepsy and a family history of epilepsy (familial acquired focal epilepsy, $n = 525$) but not in individuals with nonlesional focal epilepsy and no known family history of epilepsy (sporadic nonacquired focal epilepsy, $n = 662$) (50). In familial nonacquired focal epilepsy, five known genes ranked as the top five genes enriched for ultrarare deleterious variants (*DEPDC5*, *LGI1*, *PCDH19*, *SCN1A*, and *GRIN2A*). These results are in line with those from the Epi25 Collaborative study (51). This WES analysis of 17,606 individuals found weak enrichment in ultrarare deleterious coding variation in individuals with nonlesional focal epilepsy ($n = 5{,}331$), most of whom had sporadic nonacquired focal epilepsy (only 5% of these individuals had an affected first-degree relative).

In addition to germline variants, recent studies have indicated that somatic variants confined to the brain contribute to the hidden genetics of focal epilepsies (162). There has been a particular focus on brain somatic mutations in the mTOR pathway genes (e.g., *TSC1*, *TSC2*, *MTOR*, *PIK3CA*, *AKT3*, and *DEPDC5*), which can result in different malformations of cortical development associated with focal epilepsy, such as tuberous sclerosis complex, focal cortical dysplasia, and hemimegalencephaly (78, 90, 113). In some cases, it is the co-occurrence of a germline and a somatic mutation in negative modulators of the mTOR pathway (e.g., *TSC1*, *TSC2*, or *DEPDC5*) that leads to a malformation of cortical development (a two-hit genetic model) (39, 126). Somatic variants in genes within other pathways can also lead to brain lesions associated with focal epilepsy, including the Sonic hedgehog pathway in hypothalamic hamartomata and the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway in leptomeningeal angiomatosis in the context of Sturge–Weber syndrome or in gangliogliomas (162). Notably, recent reports have suggested that somatic variants in *SLC35A2*, encoding a UDP-galactose transporter, are implicated in focal epilepsies with and without brain lesions on MRI or neuropathology (141, 160). Interestingly, while some cases had no detectable brain lesion, pathological examination found that a subset had features of focal cortical dysplasia. It is likely that more patients will be diagnosed as having pathogenic somatic variants and that more genes will be associated with focal epilepsy by harboring disease-causing somatic variation (162).

3.5. Febrile Seizures

Febrile seizures are the most common epilepsy syndrome, affecting approximately 3% of all children under the age of 5 (138); in certain parts of the world, they may be even more frequent. They

are characterized by seizures, usually convulsive, that occur in young children (typically between ages 6 months and 5 years, although broader definitions include from 1 month to 6 years) in conjunction with fever and are not associated with central nervous system infection. In the past, they were regarded as separate from epilepsy (recurrent afebrile seizures) because febrile seizures usually have a benign outcome, and families and their physicians wanted to avoid the stigmatization associated with a diagnosis of epilepsy. In fact, the relationship of febrile seizures and epilepsy is now known to be much closer and more complex, and genetics has helped unravel these relationships. Before we review the genetics, several clinical issues warrant discussion.

3.5.1. Diagnosis of febrile seizures. With the first seizure with fever, and with any atypical recurrences, the diagnosis of cerebral infection must be considered; the vigor of investigation (lumbar puncture and imaging) will depend on the age of the child, length of the seizure, clinical state, speed of recovery, and so on. Conversely, true febrile seizures are sometimes confused with syncopal events, which can occur with high temperature (febrile syncope), and with febrile delirium, which can occur in young children with very high fevers. A final diagnostic consideration is that, particularly after a child has had a first febrile seizure, subsequent events may be similarly labeled, even in the absence of fever, particularly if the child is a little unwell—this is an error and should lead to other diagnostic considerations.

3.5.2. Outcome of febrile seizures. For true febrile seizures, approximately two-thirds of children will have a single episode and one-third will have a few recurrences, although the recurrences can occasionally be frequent (156). A longitudinal study found that 7% of children who have febrile seizures will develop recurrent afebrile seizures or epilepsy (1).

In several childhood epilepsy syndromes, onset can be preceded by febrile seizures in some children. These syndromes include self-limited childhood epilepsy with centrotemporal spikes and some GGEs. Here, it is assumed that the hyperexcitability conferred by the nascent epileptic process results in a seizure with the stimulus of fever. Some epileptic encephalopathies may present with the first seizure in association with fever, the best-known example being Dravet syndrome due to pathogenic variants in *SCN1A* (see Section 3.2.2). The disorder of febrile seizures plus (FS+) accounts for an important part of the overlap between true febrile seizures and epilepsy. FS+ refers to seizures with fever outside of the traditional boundaries of that disorder (1 month to 6 years) and/or with afebrile seizures and typically occurs as part of the familial syndrome of GEFS+ (165). In GEFS+ families, individual subjects may have febrile seizures, FS+, FS+ with additional focal or generalized seizures, or (rarely) epileptic encephalopathies (165). There is also a long-recognized but infrequent association between prolonged febrile seizures (including febrile status epilepticus) and the later development of temporal lobe epilepsy with hippocampal sclerosis. There is a complex and controversial literature on this subject, but the sequence of events of a prolonged febrile seizure leading to hippocampal swelling and hippocampal sclerosis is well established; in many children, however, it is believed there may be a preexisting abnormality of the hippocampus, and there is some evidence of genetic underpinnings. A large prospective study of febrile status (FEBSTAT) suggested that both mechanisms may be operative (98).

3.5.3. Clinical genetics of febrile seizures. Febrile seizures have a substantial genetic component with a recurrence risk ratio of approximately 4 and a high concordance (0.6) in monozygotic twins (155). Pedigrees with autosomal dominant inheritance are well known, and these are apparent even within epidemiologically ascertained samples. Segregation analyses suggest a mixture of some autosomal dominant families, with the majority demonstrating complex and presumably polygenic etiology (127).

For GEFS+, many autosomal dominant families have been described, and in approximately 30% a major gene has been identified (see below). Some GEFS+ pedigrees are more compatible with complex inheritance (109).

3.5.4. Molecular genetics. Most progress has been made in GEFS+, where pathogenic rare variants in several genes have been described in large families; some also are observed de novo. These include the sodium-channel subunit genes *SCN1A* and *SCN1B*, the GABA receptor gene *GABRG2*, and more recently the synaptic gene *STX1B* (109). Families segregating these genes may exhibit heterogeneous syndromes, ranging from febrile seizures and FS+ at the mild end to Dravet syndromes at the severe end, which presents challenges for prognostic counseling.

For pure familial febrile seizures, although studies of several large families have been published and loci reported, discovery of major dominant genes has been elusive, with the exception of rare families segregating *SCN1A* variants (93). The polygenic contribution to febrile seizures has been investigated by a Danish GWAS involving more than 3,000 children with febrile seizures and more than 5,500 controls (55). Four loci were associated with febrile seizures, harboring the sodium-channel genes *SCN1A* and *SCN2A*, a TMEM16 family gene (*ANO3*), and a region associated with magnesium levels (12q21.33). Additionally, in febrile seizures associated with immunization, the interferon-stimulated gene *IFI44L* and the measles virus receptor gene *CD46* were implicated.

4. OTHER MECHANISMS AND NEW AVENUES OF EPILEPSY GENETICS RESEARCH

4.1. Repeat Expansions

Short tandem repeats are repeats of short motifs of DNA that can be found throughout the human genome, numbering in the tens of thousands. They have previously been used as genetic markers for linkage mapping. A subset of approximately 40 short tandem repeats show evidence of expansions that have been linked to disease. Short tandem repeat expansions include repeats that have increased motif numbers in patients. The disease mechanism appears to vary, although it clusters to some extent with motif type. RNA toxicity is commonly invoked, with repeats sequestering transcription factors or leading to aberrant protein folding, more adversely affecting neuronal cells due to their long life span. Short tandem repeat expansions predominantly cause neurological disorders.

Six repeat expansions are known to cause epilepsy, and they cluster into two epilepsy disease types: (*a*) progressive myoclonus epilepsy of the Unverricht–Lundborg type [epilepsy, progressive myoclonic 1A (EPM1)], which is caused by a recessive repeat expansion located in a promoter that consists of a repeated motif of 12 base pairs (CCCCGCCCCGCG in the *CSTB* gene), and (*b*) familial adult myoclonus epilepsy (FAME), which is caused by highly expanded intronic pentamers, for which there are now five reported loci: FAME1–3 and FAME6–7. The repeat expansion for EPM1 was first described in 1997. The repeat expansions associated with different types of FAME—i.e., FAME1, FAME6, and FAME7—were first described in 2018, and those associated with FAME2, FAME3, and FAME4 were described in 2019 (24, 59, 163). It is interesting that FAME can be thought of as the mild extreme of the clinical spectrum of the progressive myoclonic epilepsies and that all six repeat expansions thus far identified for epilepsy cluster within this clinical subtype (10).

Both EPM1 and FAME1 display founder effects. EPM1 has multiple founder effects, including for Finland (83) and Reunion Island (103). FAME1 has a Japanese founder effect, with at least 60 reported families (76). Furthermore, we and others (19, 84) have shown that this repeat expansion

has a geographic range that extends throughout Asia, with FAME1 repeat expansions (all with evidence of the same core haplotype surrounding the repeat expansion in *SAMD12*) now also reported in Chinese, Sri Lankan, and Indian families. These new findings have already led to the genetic diagnosis of several hundred individuals. The dissemination of these findings and identification of other relevant repeat expansions are expected to have a major impact on the molecular diagnosis of Mendelian epilepsies and will likely affect thousands of patients. Additionally, repeat expansions represent a genetic lesion that can be targeted with precision therapies. Recent reports of successful phase 2 clinical trials of antisense oligonucleotide therapies for Huntington's disease hold promise for other repeat expansions, including those implicated in epilepsy.

The existing phenotypic overlap among the ataxias, which are still the most highly enriched set of disorders for repeat expansion, and the epilepsies (e.g., *ATXN1*, a GWAS hit for epilepsy, also contains a coding repeat expansion that causes spinocerebellar ataxia type 1) suggests that even known ataxia-related repeat expansions might act as risk factors for epilepsy, a hypothesis that requires testing in future studies. At the very least, the identification of known repeat expansions in patients with epilepsy may result in recognition of ataxia symptoms, which might have been neglected or missed in cases presenting with seizures. Until recently, the only way to test for the presence of repeat expansions was to make use of either repeat-primed PCR or Southern blot assays on a locus-by-locus basis. These assays are prohibitive in cost and effort when applied to larger cohorts, and hence such investigations have not been feasible. In the last few years, several computational methods have been developed (30, 43, 104, 150, 151) that can determine the presence of repeat expansions in standard WGS and WES (151). These algorithms can be applied to any existing WGS data from epilepsy patients to screen for intronic EPM1 and FAME expansions.

These algorithmic developments allow the analysis of WGS and WES cohorts, including large epilepsy cohorts such as the Epi25 Collaborative cohort (51), for the presence of both known and novel repeat expansions. The extent to which these well-known and novel epilepsy repeat expansions explain missing heritability in the more common epilepsies has not yet been investigated. Additional novel repeat expansion discoveries in epilepsy are also likely to come to light as the detection algorithms for repeat expansions improve further and as long-read sequencing becomes more common, ultimately making repeat expansion detection in epilepsy part of a routine analysis pipeline.

4.2. Polygenic Risk Scores

Polygenic risk scores (PRSs) are additive models for disease risk that are calculated at the individual level using the individual's genotyping results, which can be derived from SNP chips or WGS. The regression coefficients in the additive risk model are derived mostly from GWASs. The most recent GWAS for epilepsy identified 16 loci for epilepsy, which has substantially increased the power of PRSs for epilepsy to encapsulate genetic risk due to common variants (73).

The potential uses of PRSs have been outlined by others (79, 82, 95) and include (*a*) predicting disease risk for individual patients; (*b*) estimating heritability, including missing heritability, to allow the determination of the genetic complexity of a disease; and (*c*) enabling causal investigation with Mendelian randomization. Mendelian randomization examines the ability of PRSs from one trait to predict the PRSs of another trait. Due to the randomization of alleles in individuals, this method allows causal inferences rather than mere correlation analysis (31). It is being increasingly applied to complex traits, teasing apart and identifying underpinning driver biological mechanisms (89).

With the development of the first truly powerful GWAS (and hence predictive PRSs) for epilepsy, it is now possible to use PRSs to investigate diverse hypotheses for epilepsy. The ILAE

Consortium on Complex Epilepsies determined, based on linkage disequilibrium score regression, that epilepsy shares little genetic risk with neuropsychiatric conditions such as schizophrenia, bipolar disorders, and autism, which tend to share much more genetic risk with each other (73). These recent GWAS results can also be combined with other GWAS results, such as those from the UK Biobank, to infer likely causal drivers of epilepsy, allowing many of the previously hypothesized contributors to be investigated using the Mendelian randomization framework. Epilepsy PRS investigations and applications are in their infancy. One recent large study confirmed the initial PRS findings in well-phenotyped cohorts derived largely from European ancestries but showed that cohorts from other ethnicities and cohorts where phenotyping was imprecise had less robust replication (88). PRSs may emerge as clinically useful in the near future, but close attention to phenotyping and ethnicity will be needed.

4.3. Oligogenic Models

Here, we define oligogenic models as genetic models where more than one allele is required to influence genetic risk. These models include modifier genes, or epistasis, where neither of two variants individually contributes to the genetic risk; rather, the presence of both variants is required to change the risk. As discussed in previous sections, current methodologies for the analysis of genetic data either focus only on additive risks or impose filters that likely remove variants that could have oligogenic roles. Hence, modifier genes are likely to be filtered out since modifier variants are likely to have a higher frequency. Epistasis effects are not explicitly evaluated in GWASs because of the large number of models requiring evaluation, imposing a severe multiple-testing burden. However, these models are tantalizing for epilepsy since there is already evidence that epilepsy genetic risk is in part attributable to oligogenic contributions.

First, a known, highly penetrant, human monogenic cause of human epilepsy, such as the g2(R43Q) $GABA_A$ variant, has been demonstrated to have different susceptibility to thermal seizures depending on the inbred mouse strain into which the mutation was introduced, suggesting that the genetic background contains additional genetic factors (125). This is an example of a rare-variant–common-complex genetic risk combination.

Second, there are biological reasons for assuming the existence of oligogenic models. Several epilepsy genes code for subunits of ion channels, such as voltage-gated sodium channels (e.g., *SCN1A* and *SCN1B*), voltage-gated potassium channels (e.g., *KCNQ2* and *KCNQ3*), and ligand-gated ion channels (e.g., *CHRNA4*, *GABRG2*, and *GABRA1*) (115). Thus, it is conceivable that specific variants that are in different subunits but in the same ion channel could jointly be pathogenic, but not pathogenic on their own. This is an example of potential epistatic interaction.

Modifiers to the ion channels also appear highly plausible. An *SCNA8A* modifier effect has already been demonstrated for a chemically induced epilepsy *SCN1A* heterozygous knockout mouse (96).

Large epilepsy cohorts, such as those assembled by the Epi25 Collaborative (51), Epi4K Consortium (47, 48), and ILAE Consortium on Complex Epilepsies (72, 73), will now permit hypothesis testing to investigate specific oligogenic models. Exhaustive, genome-wide-scale analysis testing of oligogenic models is not feasible due to the large number of tests that would need to be performed, leading to severe multiple-testing penalties. Oligogenic hypotheses can also be further evaluated in mouse models or with methods such as deep mutational scanning.

5. CONCLUSIONS

Over the past decade, there has been tremendous progress in the field of epilepsy genetics. This progress has been driven mainly by advances in sequencing technologies and computational

approaches, as well as by the establishment of large international collaborations (47, 51, 73). A major breakthrough has been the unraveling of the molecular genetics—particularly the role of de novo mutagenesis—in the DEEs, a group of disorders long considered to be largely acquired, resulting from pre-, peri-, or postnatal insults. Important developments have also occurred in the understanding of the genetic underpinnings of two common epilepsy groups—the focal epilepsies and the GGEs. Nonacquired focal epilepsies appear to be caused mainly by rare variants, with minimal contributions from common variants. Conversely, in the GGEs, common variants are emerging as having a more important role than rare variants.

Novel analytical approaches are being developed, some of which may uncover hidden genetic mechanisms. For example, single-cell RNA sequencing technologies map gene expression at single-cell resolution, allowing one to identify different cell populations, uncover regulatory relationships between genes, and track the trajectories of distinct cell lineages in development (71). The application of single-cell RNA sequencing to brain tissue from people with epilepsy, obtained from epilepsy surgical resections or postmortem, may shed light on pathogenic processes.

Ongoing large international collaborations will further our understanding of the genetic landscape of epilepsy. Existing data sets comprising thousands of sequenced or genotyped epilepsy samples can also be interrogated using novel approaches or even merged with large-scale external data resources, such as the ENCODE, UK Biobank, or Genotype-Tissue Expression (GTEx) database. The comparison of epilepsy genomic data with those from other diseases and traits may result in the identification of shared mechanisms or pathways. Clearly, there are unprecedented opportunities for hypothesis generation and testing.

The wealth of progress in epilepsy genetics is already affecting clinical practice. Detecting a pathogenic variant in an epilepsy gene is important for counseling patients and caregivers about disease prognosis and family planning and can guide clinical management (121). It is also a prerequisite for personalized treatment approaches, either through drug repurposing or by designing and developing novel precise therapies (121). PRSs may soon venture into clinical application and allow incorporation of common variations, alongside rare variants, in the management of individuals with epilepsy.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

We thank John Tay, who created **Figure 2** based on our instructions.

LITERATURE CITED

1. Annegers JF, Hauser WA, Shirts SB, Kurland LT. 1987. Factors prognostic of unprovoked seizures after febrile convulsions. *N. Engl. J. Med.* 316:493–98
2. Arsov T, Mullen SA, Damiano JA, Lawrence KM, Huh LL, et al. 2012. Early onset absence epilepsy: 1 in 10 cases is caused by GLUT1 deficiency. *Epilepsia* 53:e204–7
3. Arsov T, Mullen SA, Rogers S, Phillips AM, Lawrence KM, et al. 2012. Glucose transporter 1 deficiency in the idiopathic generalized epilepsies. *Ann. Neurol.* 72:807–15
4. Bailey JN, de Nijs L, Bai D, Suzuki T, Miyamoto H, et al. 2018. Variant intestinal-cell kinase in juvenile myoclonic epilepsy. *N. Engl. J. Med.* 378:1018–28
5. Baldassari S, Picard F, Verbeek NE, van Kempen M, Brilstra EH, et al. 2019. The landscape of epilepsy-related GATOR1 variants. *Genet. Med.* 21:398–408

6. Balestrini S, Milh M, Castiglioni C, Luthy K, Finelli MJ, et al. 2016. TBC1D24 genotype-phenotype correlation: epilepsies and other neurologic features. *Neurology* 87:77–85
7. Barcia G, Fleming MR, Deligniere A, Gazula VR, Brown MR, et al. 2012. De novo gain-of-function *KCNT1* channel mutations cause malignant migrating partial seizures of infancy. *Nat. Genet.* 44:1255–59
8. Baulac S. 2016. mTOR signaling pathway genes in focal epilepsies. *Prog. Brain Res.* 226:61–79
9. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, et al. 2010. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 51:676–85
10. Berkovic SF. 2008. Progressive myoclonus epilepsies. In *Epilepsy: A Comprehensive Textbook*, ed. JJ Engel, TA Pedley, pp. 2525–35. Philadelphia: Lippincott Williams & Wilkins. 2nd ed.
11. Berkovic SF, Howell RA, Hay DA, Hopper JL. 1998. Epilepsies in twins: genetics of the major epilepsy syndromes. *Ann. Neurol.* 43:435–45
12. Berkovic SF, McIntosh A, Howell RA, Mitchell A, Sheffield LJ, Hopper JL. 1996. Familial temporal lobe epilepsy: a common disorder identified in twins. *Ann. Neurol.* 40:227–35
13. Burgess R, Wang S, McTague A, Boysen KE, Yang X, et al. 2019. The genetic landscape of epilepsy of infancy with migrating focal seizures. *Ann. Neurol.* 86:821–31
14. Campeau PM, Kasperaviciute D, Lu JT, Burrage LC, Kim C, et al. 2014. The genetic basis of DOORS syndrome: an exome-sequencing study. *Lancet Neurol.* 13:44–58
15. Carvill GL, Engel KL, Ramamurthy A, Cochran JN, Roovers J, et al. 2018. Aberrant inclusion of a poison exon causes Dravet syndrome and related *SCN1A*-associated genetic epilepsies. *Am. J. Hum. Genet.* 103:1022–29
16. Carvill GL, Heavin SB, Yendle SC, McMahon JM, O'Roak BJ, et al. 2013a. Targeted resequencing in epileptic encephalopathies identifies de novo mutations in *CHD2* and *SYNGAP1*. *Nat. Genet.* 45:825–30
17. Carvill GL, Regan BM, Yendle SC, O'Roak BJ, Lozovaya N, et al. 2013b. *GRIN2A* mutations cause epilepsy-aphasia spectrum disorders. *Nat. Genet.* 45:1073–76
18. Cavalleri GL, Lynch JM, Depondt C, Burley MW, Wood NW, et al. 2005. Failure to replicate previously reported genetic associations with sporadic temporal lobe epilepsy: where to from here? *Brain* 128:1832–40
19. Cen Z, Jiang Z, Chen Y, Zheng X, Xie F, et al. 2018. Intronic pentanucleotide TTTCA repeat insertion in the *SAMD12* gene causes familial cortical myoclonic tremor with epilepsy type 1. *Brain* 141:2280–88
20. Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M. 2009. Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study. *Lancet* 373:1105–10
21. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. 2001. De novo mutations in the sodium-channel gene *SCN1A* cause severe myoclonic epilepsy of infancy. *Am. J. Hum. Genet.* 68:1327–32
22. Cooper MS, McIntosh A, Crompton DE, McMahon JM, Schneider A, et al. 2016. Mortality in Dravet syndrome. *Epilepsy Res.* 128:43–47
23. Corbett MA, Bellows ST, Li M, Carroll R, Micallef S, et al. 2016. Dominant *KCNA2* mutation causes episodic ataxia and pharmacoresponsive epilepsy. *Neurology* 87:1975–84
24. Corbett MA, Kroes T, Veneziano L, Bennett MF, Florian R, et al. 2019. Intronic ATTTC repeat expansions in *STARD7* in familial adult myoclonic epilepsy linked to chromosome 2. *Nat. Commun.* 10:4920
25. Corey LA, Berg K, Pellock JM, Solaas MH, Nance WE, DeLorenzo RJ. 1991. The occurrence of epilepsy and febrile seizures in Virginian and Norwegian twins. *Neurology* 41:1433–36
26. Corey LA, Pellock JM, Kjeldsen MJ, Nakken KO. 2011. Importance of genetic factors in the occurrence of epilepsy syndrome type: a twin study. *Epilepsy Res.* 97:103–11
27. Cossette P, Liu L, Brisebois K, Dong H, Lortie A, et al. 2002. Mutation of *GABRA1* in an autosomal dominant form of juvenile myoclonic epilepsy. *Nat. Genet.* 31:184–89
28. Curatolo P, Moavero R, de Vries PJ. 2015. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. *Lancet Neurol.* 14:733–45
29. Daber RD, Conlin LK, Leonard LD, Canevini MP, Vignoli A, et al. 2012. Ring chromosome 20. *Eur. J. Med. Genet.* 55:381–87

30. Dashnow H, Lek M, Phipson B, Halman A, Sadedin S, et al. 2018. STRetch: detecting and discovering pathogenic short tandem repeat expansions. *Genome Biol*. 19:121
31. Davies NM, Holmes MV, Davey Smith G. 2018. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ* 362:k601
32. Dazzo E, Fanciulli M, Serioli E, Minervini G, Pulitano P, et al. 2015. Heterozygous reelin mutations cause autosomal-dominant lateral temporal epilepsy. *Am. J. Hum. Genet.* 96:992–1000
33. Dazzo E, Rehberg K, Michelucci R, Passarelli D, Boniver C, et al. 2018. Mutations in *MICAL-1* cause autosomal-dominant lateral temporal epilepsy. *Ann. Neurol.* 83:483–93
34. de Kovel CG, Trucks H, Helbig I, Mefford HC, Baker C, et al. 2010. Recurrent microdeletions at 15q11.2 and 16p13.11 predispose to idiopathic generalized epilepsies. *Brain* 133:23–32
35. de Lange KM, Moutsianas L, Lee JC, Lamb CA, Luo Y, et al. 2017. Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nat. Genet.* 49:256–61
36. De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI. 1991. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. *N. Engl. J. Med.* 325:703–9
37. Depienne C, Arzimanoglou A, Trouillard O, Fedirko E, Baulac S, et al. 2006. Parental mosaicism can cause recurrent transmission of *SCN1A* mutations associated with severe myoclonic epilepsy of infancy. *Hum. Mutat.* 27:389
38. Devinsky O, Vezzani A, O'Brien TJ, Jette N, Scheffer IE, et al. 2018. Epilepsy. *Nat. Rev. Dis. Primers* 4:18024
39. D'Gama AM, Woodworth MB, Hossain AA, Bizzotto S, Hatem NE, et al. 2017. Somatic mutations activating the mTOR pathway in dorsal telencephalic progenitors cause a continuum of cortical dysplasias. *Cell Rep*. 21:3754–66
40. Dibbens LM, de Vries B, Donatello S, Heron SE, Hodgson BL, et al. 2013. Mutations in *DEPDC5* cause familial focal epilepsy with variable foci. *Nat. Genet.* 45:546–51
41. Dibbens LM, Mullen S, Helbig I, Mefford HC, Bayly MA, et al. 2009. Familial and sporadic 15q13.3 microdeletions in idiopathic generalized epilepsy: precedent for disorders with complex inheritance. *Hum. Mol. Genet.* 18:3626–31
42. Dibbens LM, Tarpey PS, Hynes K, Bayly MA, Scheffer IE, et al. 2008. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. *Nat. Genet.* 40:776–81
43. Dolzhenko E, van Vugt J, Shaw RJ, Bekritsky MA, van Blitterswijk M, et al. 2017. Detection of long repeat expansions from PCR-free whole-genome sequence data. *Genome Res*. 27:1895–903
44. Dravet C. 2011. The core Dravet syndrome phenotype. *Epilepsia* 52(Suppl. 2):3–9
45. Ellis CA, Petrovski S, Berkovic SF. 2020. Epilepsy genetics: clinical impacts and biological insights. *Lancet Neurol*. 19:93–100
46. Emdin CA, Khera AV, Kathiresan S. 2017. Mendelian randomization. *JAMA* 318:1925–26
47. Epi4K Consort. 2012. Epi4K: gene discovery in 4,000 genomes. *Epilepsia* 53:1457–67
48. Epi4K Consort. 2017. Phenotypic analysis of 303 multiplex families with common epilepsies. *Brain* 140:2144–56
49. Epi4K Consort., Epilepsy Phenome/Genome Proj. 2013. De novo mutations in epileptic encephalopathies. *Nature* 501:217–21
50. Epi4K Consort., Epilepsy Phenome/Genome Proj. 2017. Ultra-rare genetic variation in common epilepsies: a case-control sequencing study. *Lancet Neurol.* 16:135–43
51. Epi25 Collab. 2019. Ultra-rare genetic variation in the epilepsies: a whole-exome sequencing study of 17,606 individuals. *Am. J. Hum. Genet.* 105:267–82
52. Epicure Consort., EMINet Consort., Steffens M, Leu C, Ruppert AK, et al. 2012. Genome-wide association analysis of genetic generalized epilepsies implicates susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32. *Hum. Mol. Genet.* 21:5359–72
53. Eriksson H, Wirdefeldt K, Asberg S, Zelano J. 2019. Family history increases the risk of late seizures after stroke. *Neurology* 93:e1964–70
54. Espinosa-Jovel C, Toledano R, Aledo-Serrano A, Garcia-Morales I, Gil-Nagel A. 2018. Epidemiological profile of epilepsy in low income populations. *Seizure* 56:67–72

55. Feenstra B, Pasternak B, Geller F, Carstensen L, Wang T, et al. 2014. Common variants associated with general and MMR vaccine-related febrile seizures. *Nat. Genet.* 46:1274–82
56. Ferreira MAR, Mathur R, Vonk JM, Szwajda A, Brumpton B, et al. 2019. Genetic architectures of childhood- and adult-onset asthma are partly distinct. *Am. J. Hum. Genet.* 104:665–84
57. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, et al. 2017. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 58:522–30
58. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, et al. 2005. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 46:470–72
59. Florian RT, Kraft F, Leitao E, Kaya S, Klebe S, et al. 2019. Unstable TTTTA/TTTCA expansions in *MARCH6* are associated with familial adult myoclonic epilepsy type 3. *Nat. Commun.* 10:4919
60. Fritsche LG, Igl W, Bailey JN, Grassmann F, Sengupta S, et al. 2016. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. *Nat. Genet.* 48:134–43
61. Gilliam F. 2002. Optimizing health outcomes in active epilepsy. *Neurology* 58:S9–20
62. Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, et al. 2016. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat. Genet.* 48:856–66
63. Grinton BE, Heron SE, Pelekanos JT, Zuberi SM, Kivity S, et al. 2015. Familial neonatal seizures in 36 families: Clinical and genetic features correlate with outcome. *Epilepsia* 56:1071–80
64. Hauser WA, Annegers JF, Kurland LT. 1993. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia* 34:453–68
65. Helbig I, Mefford HC, Sharp AJ, Guipponi M, Fichera M, et al. 2009. 15q13.3 microdeletions increase risk of idiopathic generalized epilepsy. *Nat. Genet.* 41:160–62
66. Helbig KL, Farwell Hagman KD, Shinde DN, Mroske C, Powis Z, et al. 2016. Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genet. Med.* 18:898–905
67. Heron SE, Smith KR, Bahlo M, Nobili L, Kahana E, et al. 2012. Missense mutations in the sodium-gated potassium channel gene *KCNT1* cause severe autosomal dominant nocturnal frontal lobe epilepsy. *Nat. Genet.* 44:1188–90
68. Hesdorffer DC, Logroscino G, Benn EK, Katri N, Cascino G, Hauser WA. 2011. Estimating risk for developing epilepsy: a population-based study in Rochester, Minnesota. *Neurology* 76:23–27
69. Hildebrand MS, Harvey AS, Malone S, Damiano JA, Do H, et al. 2018. Somatic *GNAQ* mutation in the *forme fruste* of Sturge-Weber syndrome. *Neurol Genet*. 4:e236
70. Howell KB, Eggers S, Dalziel K, Riseley J, Mandelstam S, et al. 2018. A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy. *Epilepsia* 59:1177–87
71. Hwang B, Lee JH, Bang D. 2018. Single-cell RNA sequencing technologies and bioinformatics pipelines. *Exp. Mol. Med.* 50:96
72. Int. League Against Epilepsy Consort. Complex Epilepsies. 2014. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. *Lancet Neurol.* 13:893–903
73. Int. League Against Epilepsy Consort. Complex Epilepsies. 2018. Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies. *Nat. Commun.* 9:5269
74. Int. Mult. Scler. Genet. Consort. 2013. Analysis of immune-related loci identifies 48 new susceptibility variants for multiple sclerosis. *Nat. Genet.* 45:1353–60
75. Ishida S, Picard F, Rudolf G, Noe E, Achaz G, et al. 2013. Mutations of *DEPDC5* cause autosomal dominant focal epilepsies. *Nat. Genet.* 45:552–55
76. Ishiura H, Doi K, Mitsui J, Yoshimura J, Matsukawa MK, et al. 2018. Expansions of intronic TTTCA and TTTTA repeats in benign adult familial myoclonic epilepsy. *Nat. Genet.* 50:581–90
77. Jallon P, Latour P. 2005. Epidemiology of idiopathic generalized epilepsies. *Epilepsia* 46(Suppl. 9):10–14
78. Jamuar SS, Lam AT, Kircher M, D'Gama AM, Wang J, et al. 2014. Somatic mutations in cerebral cortical malformations. *N. Engl. J. Med.* 371:733–43

79. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, et al. 2018. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat. Genet.* 50:1219–24
80. Lal D, Reinthaler EM, Schubert J, Muhle H, Riesch E, et al. 2014. *DEPDC5* mutations in genetic focal epilepsies of childhood. *Ann. Neurol.* 75:788–92
81. Lam M, Hill WD, Trampush JW, Yu J, Knowles E, et al. 2019. Pleiotropic meta-analysis of cognition, education, and schizophrenia differentiates roles of early neurodevelopmental and adult synaptic pathways. *Am. J. Hum. Genet.* 105:334–50
82. Lee JJ, Wedow R, Okbay A, Kong E, Maghzian O, et al. 2018. Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nat. Genet.* 50:1112–21
83. Lehesjoki AE, Koskiniemi M. 1999. Progressive myoclonus epilepsy of Unverricht-Lundborg type. *Epilepsia* 40(Suppl. 3):23–28
84. Lei XX, Liu Q, Lu Q, Huang Y, Zhou XQ, et al. 2019. TTTCA repeat expansion causes familial cortical myoclonic tremor with epilepsy. *Eur. J. Neurol.* 26:513–18
85. Lemke JR, Lal D, Reinthaler EM, Steiner I, Nothnagel M, et al. 2013. Mutations in *GRIN2A* cause idiopathic focal epilepsy with rolandic spikes. *Nat. Genet.* 45:1067–72
86. Lerche H, Berkovic SF, Lowenstein DH, EuroEPINOMICS-CoGIE Consort., EpiPGX Consort., Epi4K Consort./Epilepsy Phenome/Genome Proj. Collab. 2019. Intestinal-cell kinase and juvenile myoclonic epilepsy. *N. Engl. J. Med.* 380:e24
87. Lesca G, Rudolf G, Bruneau N, Lozovaya N, Labalme A, et al. 2013. *GRIN2A* mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. *Nat. Genet.* 45:1061–66
88. Leu C, Stevelink R, Smith AW, Goleva SB, Kanai M, et al. 2019. Polygenic burden in focal and generalized epilepsies. *Brain* 142:3473–81
89. Ligthart S, Vaez A, Vosa U, Stathopoulou MG, de Vries PS, et al. 2018. Genome analyses of >200,000 individuals identify 58 loci for chronic inflammation and highlight pathways that link inflammation and complex disorders. *Am. J. Hum. Genet.* 103:691–706
90. Lim JS, Kim WI, Kang HC, Kim SH, Park AH, et al. 2015. Brain somatic mutations in *MTOR* cause focal cortical dysplasia type II leading to intractable epilepsy. *Nat. Med.* 21:395–400
91. Luo Y, Hitz BC, Gabdank I, Hilton JA, Kagda MS, et al. 2020. New developments on the Encyclopedia of DNA Elements (ENCODE) data portal. *Nucleic Acids Res.* 48:D882–89
92. Maljevic S, Møller RS, Reid CA, Pérez-Palma E, Lal D, et al. 2019. Spectrum of $GABA_A$ receptor variants in epilepsy. *Curr. Opin. Neurol.* 32:183–90
93. Mantegazza M, Gambardella A, Rusconi R, Schiavon E, Annesi F, et al. 2005. Identification of an $Na_v1.1$ sodium channel (SCN1A) loss-of-function mutation associated with familial simple febrile seizures. *PNAS* 102:18177–82
94. Marini C, Scheffer IE, Nabbout R, Suls A, De Jonghe P, et al. 2011. The genetics of Dravet syndrome. *Epilepsia* 52(Suppl. 2):24–29
95. Martin AR, Daly MJ, Robinson EB, Hyman SE, Neale BM. 2019. Predicting polygenic risk of psychiatric disorders. *Biol. Psychiatry* 86:97–109
96. Martin MS, Tang B, Papale LA, Yu FH, Catterall WA, Escayg A. 2007. The voltage-gated sodium channel *Scn8a* is a genetic modifier of severe myoclonic epilepsy of infancy. *Hum. Mol. Genet.* 16:2892–99
97. May P, Girard S, Harrer M, Bobbili DR, Schubert J, et al. 2018. Rare coding variants in genes encoding $GABA_A$ receptors in genetic generalised epilepsies: an exome-based case-control study. *Lancet Neurol.* 17:699–708
98. McClelland AC, Gomes WA, Shinnar S, Hesdorffer DC, Bagiella E, et al. 2016. Quantitative evaluation of medial temporal lobe morphology in children with febrile status epilepticus: results of the FEBSTAT study. *Am. J. Neuroradiol.* 37:2356–62
99. McTague A, Howell KB, Cross JH, Kurian MA, Scheffer IE. 2016. The genetic landscape of the epileptic encephalopathies of infancy and childhood. *Lancet Neurol.* 15:304–16

100. Mefford HC, Muhle H, Ostertag P, von Spiczak S, Buysse K, et al. 2010. Genome-wide copy number variation in epilepsy: novel susceptibility loci in idiopathic generalized and focal epilepsies. *PLOS Genet*. 6:e1000962
101. Mefford HC, Yendle SC, Hsu C, Cook J, Geraghty E, et al. 2011. Rare copy number variants are an important cause of epileptic encephalopathies. *Ann. Neurol.* 70:974–85
102. Michelucci R, Poza JJ, Sofia V, de Feo MR, Binelli S, et al. 2003. Autosomal dominant lateral temporal epilepsy: clinical spectrum, new epitempin mutations, and genetic heterogeneity in seven European families. *Epilepsia* 44:1289–97
103. Moulard B, Darcel F, Mignard D, Jeanpierre M, Genton P, et al. 2003. Founder effect in patients with Unverricht-Lundborg disease on reunion island. *Epilepsia* 44:1357–60
104. Mousavi N, Shleizer-Burko S, Yanicky R, Gymrek M. 2019. Profiling the genome-wide landscape of tandem repeat expansions. *Nucleic Acids Res*. 47:e90
105. Mullen SA, Berkovic SF (ILAE Genet. Comm.). 2018. Genetic generalized epilepsies. *Epilepsia* 59:1148–53
106. Mullen SA, Carvill GL, Bellows S, Bayly MA, Trucks H, et al. 2013. Copy number variants are frequent in genetic generalized epilepsy with intellectual disability. *Neurology* 81:1507–14
107. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, et al. 2012. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380:2197–223
108. Myers CT, Hollingsworth G, Muir AM, Schneider AL, Thuesmunn Z, et al. 2018a. Parental mosaicism in "de novo" epileptic encephalopathies. *N. Engl. J. Med.* 378:1646–48
109. Myers KA, Scheffer IE, Berkovic SF (ILAE Genet. Comm.). 2018b. Genetic literacy series: genetic epilepsy with febrile seizures *plus*. *Epileptic Disord*. 20:232–38
110. Nashabat M, Al Qahtani XS, Almakdob S, Altwaijri W, Ba-Armah DM, et al. 2019. The landscape of early infantile epileptic encephalopathy in a consanguineous population. *Seizure* 69:154–72
111. Nazarian A, Yashin AI, Kulminski AM. 2019. Genome-wide analysis of genetic predisposition to Alzheimer's disease and related sex disparities. *Alzheimer's Res. Ther.* 11:5
112. Nicolas A, Kenna KP, Renton AE, Ticozzi N, Faghri F, et al. 2018. Genome-wide analyses identify *KIF5A* as a novel ALS gene. *Neuron* 97:1268–83.e6
113. Niestroj LM, May P, Artomov M, Kobow K, Coras R, et al. 2019. Assessment of genetic variant burden in epilepsy-associated brain lesions. *Eur. J. Hum. Genet.* 27:1738–44
114. Ottman R, Risch N, Hauser WA, Pedley TA, Lee JH, et al. 1995. Localization of a gene for partial epilepsy to chromosome 10q. *Nat. Genet.* 10:56–60
115. Oyrer J, Maljevic S, Scheffer IE, Berkovic SF, Petrou S, Reid CA. 2018. Ion channels in genetic epilepsy: from genes and mechanisms to disease-targeted therapies. *Pharmacol. Rev.* 70:142–73
116. Papuc SM, Abela L, Steindl K, Begemann A, Simmons TL, et al. 2019. The role of recessive inheritance in early-onset epileptic encephalopathies: a combined whole-exome sequencing and copy number study. *Eur. J. Hum. Genet.* 27:408–21
117. Pelc K, Boyd SG, Cheron G, Dan B. 2008. Epilepsy in Angelman syndrome. *Seizure* 17:211–17
118. Peljto AL, Barker-Cummings C, Vasoli VM, Leibson CL, Hauser WA, et al. 2014. Familial risk of epilepsy: a population-based study. *Brain* 137:795–805
119. Perucca P. 2018. Genetics of focal epilepsies: What do we know and where are we heading? *Epilepsy Curr*. 18:356–62
120. Perucca P, Crompton DE, Bellows ST, McIntosh AM, Kalincik T, et al. 2017. Familial mesial temporal lobe epilepsy and the borderland of deja vu. *Ann. Neurol.* 82:166–76
121. Perucca P, Perucca E. 2019. Identifying mutations in epilepsy genes: impact on treatment selection. *Epilepsy Res*. 152:18–30
122. Picard F, Makrythanasis P, Navarro V, Ishida S, de Bellescize J, et al. 2014. *DEPDC5* mutations in families presenting as autosomal dominant nocturnal frontal lobe epilepsy. *Neurology* 82:2101–6
123. Poduri A, Evrony GD, Cai X, Walsh CA. 2013. Somatic mutation, genomic variation, and neurological disease. *Science* 341:1237758
124. Pueschel SM, Louis S, McKnight P. 1991. Seizure disorders in Down syndrome. *Arch. Neurol.* 48:318–20

125. Reid CA, Kim T, Phillips AM, Low J, Berkovic SF, et al. 2013. Multiple molecular mechanisms for a single $GABA_A$ mutation in epilepsy. *Neurology* 80:1003–8
126. Ribierre T, Deleuze C, Bacq A, Baldassari S, Marsan E, et al. 2018. Second-hit mosaic mutation in mTORC1 repressor DEPDC5 causes focal cortical dysplasia-associated epilepsy. *J. Clin. Investig.* 128:2452–58
127. Rich SS, Annegers JF, Hauser WA, Anderson VE. 1987. Complex segregation analysis of febrile convulsions. *Am. J. Hum. Genet.* 41:249–57
128. Ricos MG, Hodgson BL, Pippucci T, Saidin A, Ong YS, et al. 2016. Mutations in the mammalian target of rapamycin pathway regulators *NPRL2* and *NPRL3* cause focal epilepsy. *Ann. Neurol.* 79:120–31
129. Rubboli G, Plazzi G, Picard F, Nobili L, Hirsch E, et al. 2019. Mild malformations of cortical development in sleep-related hyper motor epilepsy due to *KCNT1* mutations. *Ann. Clin. Transl. Neurol.* 6:386–91
130. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, et al. 2017. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 58:512–21
131. Scheffer IE, Bhatia KP, Lopes-Cendes I, Fish DR, Marsden CD, et al. 1995. Autosomal dominant nocturnal frontal lobe epilepsy: a distinctive clinical disorder. *Brain* 118:61–73
132. Scheffer IE, Heron SE, Regan BM, Mandelstam S, Crompton DE, et al. 2014. Mutations in mammalian target of rapamycin regulator *DEPDC5* cause focal epilepsy with brain malformations. *Ann. Neurol.* 75:782–87
133. Scheffer IE, Phillips HA, O'Brien CE, Saling MM, Wrennall JA, et al. 1998. Familial partial epilepsy with variable foci: a new partial epilepsy syndrome with suggestion of linkage to chromosome 2. *Ann. Neurol.* 44:890–99
134. Schizophr. Work. Group Psychiatr. Genom. Consort. 2014. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511:421–27
135. Seidner G, Alvarez MG, Yeh JI, O'Driscoll KR, Klepper J, et al. 1998. GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. *Nat. Genet.* 18:188–91
136. Shaw M, Winczewska-Wiktor A, Badura-Stronka M, Koirala S, Gardner A, et al. 2020. Exome report: novel mutation in *ATP6V1B2* segregating with autosomal dominant epilepsy, intellectual disability and mild gingival and nail abnormalities. *Eur. J. Med. Genet.* 63:103799
137. Shellhaas RA, Wusthoff CJ, Tsuchida TN, Glass HC, Chu CJ, et al. 2017. Profile of neonatal epilepsies: characteristics of a prospective US cohort. *Neurology* 89:893–99
138. Shinnar S, Glauser TA. 2002. Febrile seizures. *J. Child Neurol.* 17(Suppl. 1):S44–52
139. Shirley MD, Tang H, Gallione CJ, Baugher JD, Frelin LP, et al. 2013. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in *GNAQ. N. Engl. J. Med.* 368:1971–79
140. Sim NS, Ko A, Kim WK, Kim SH, Kim JS, et al. 2019. Precise detection of low-level somatic mutation in resected epilepsy brain tissue. *Acta Neuropathol.* 138:901–12
141. Sim NS, Seo Y, Lim JS, Kim WK, Son H, et al. 2018. Brain somatic mutations in *SLC35A2* cause intractable epilepsy with aberrant N-glycosylation. *Neurol. Genet.* 4:e294
142. Speed D, Balding DJ. 2019. SumHer better estimates the SNP heritability of complex traits from summary statistics. *Nat. Genet.* 51:277–84
143. Steel D, Symonds JD, Zuberi SM, Brunklaus A. 2017. Dravet syndrome and its mimics: beyond *SCN1A*. *Epilepsia* 58:1807–16
144. Steinlein OK, Mulley JC, Propping P, Wallace RH, Phillips HA, et al. 1995. A missense mutation in the neuronal nicotinic acetylcholine receptor α4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. *Nat. Genet.* 11:201–3
145. Strehlow V, Heyne HO, Vlaskamp DRM, Marwick KFM, Rudolf G, et al. 2019. *GRIN2A*-related disorders: genotype and functional consequence predict phenotype. *Brain* 142:80–92
146. Strømme P, Mangelsdorf ME, Shaw MA, Lower KM, Lewis SM, et al. 2002. Mutations in the human ortholog of *Aristaless* cause X-linked mental retardation and epilepsy. *Nat. Genet.* 30:441–45

147. Suls A, Dedeken P, Goffin K, Van Esch H, Dupont P, et al. 2008. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in *SLC2A1*, encoding the glucose transporter GLUT1. *Brain* 131:1831–44
148. Suls A, Mullen SA, Weber YG, Verhaert K, Ceulemans B, et al. 2009. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. *Ann. Neurol.* 66:415–19
149. Takata A, Nakashima M, Saitsu H, Mizuguchi T, Mitsuhashi S, et al. 2019. Comprehensive analysis of coding variants highlights genetic complexity in developmental and epileptic encephalopathy. *Nat. Commun.* 10:2506
150. Tang H, Kirkness EF, Lippert C, Biggs WH, Fabani M, et al. 2017. Profiling of short-tandem-repeat disease alleles in 12,632 human whole genomes. *Am. J. Hum. Genet.* 101:700–15
151. Tankard RM, Bennett MF, Degorski P, Delatycki MB, Lockhart PJ, Bahlo M. 2018. Detecting expansions of tandem repeats in cohorts sequenced with short-read sequencing data. *Am. J. Hum. Genet.* 103:858–73
152. Thomas RH, Berkovic SF. 2014. The hidden genetics of epilepsy—a clinically important new paradigm. *Nat. Rev. Neurol.* 10:283–92
153. Tinuper P, Bisulli F, Cross JH, Hesdorffer D, Kahane P, et al. 2016. Definition and diagnostic criteria of sleep-related hyper motor epilepsy. *Neurology* 86:1834–42
154. Turley P, Walters RK, Maghzian O, Okbay A, Lee JJ, et al. 2018. Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat. Genet.* 50:229–37
155. Vadlamudi L, Milne RL, Lawrence K, Heron SE, Eckhaus J, et al. 2014. Genetics of epilepsy: the testimony of twins in the molecular era. *Neurology* 83:1042–48
156. Verity CM, Butler NR, Golding J. 1985. Febrile convulsions in a national cohort followed up from birth. I—Prevalence and recurrence in the first five years of life. *Br. Med. J. (Clin. Res. Ed.)* 290:1307–10
157. Wainberg M, Sinnott-Armstrong N, Mancuso N, Barbeira AN, Knowles DA, et al. 2019. Opportunities and challenges for transcriptome-wide association studies. *Nat. Genet.* 51:592–99
158. Wallace RH, Marini C, Petrou S, Harkin LA, Bowser DN, et al. 2001. Mutant $GABA_A$ receptor γ2-subunit in childhood absence epilepsy and febrile seizures. *Nat. Genet.* 28:49–52
159. Willer CJ, Li Y, Abecasis GR. 2010. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* 26:2190–91
160. Winawer MR, Griffin NG, Samanamud J, Baugh EH, Rathakrishnan D, et al. 2018. Somatic *SLC35A2* variants in the brain are associated with intractable neocortical epilepsy. *Ann. Neurol.* 83:1133–46
161. Xue A, Wu Y, Zhu Z, Zhang F, Kemper KE, et al. 2018. Genome-wide association analyses identify 143 risk variants and putative regulatory mechanisms for type 2 diabetes. *Nat. Commun.* 9:2941
162. Ye Z, McQuillan L, Poduri A, Green TE, Matsumoto N, et al. 2019. Somatic mutation: the hidden genetics of brain malformations and focal epilepsies. *Epilepsy Res.* 155:106161
163. Yeetong P, Pongpanich M, Srichomthong C, Assawapitaksakul A, Shotelersuk V, et al. 2019. TTTCA repeat insertions in an intron of *YEATS2* in benign adult familial myoclonic epilepsy type 4. *Brain* 142:3360–66
164. Young AI. 2019. Solving the missing heritability problem. *PLOS Genet.* 15:e1008222
165. Zhang YH, Burgess R, Malone JP, Glubb GC, Helbig KL, et al. 2017. Genetic epilepsy with febrile seizures plus: refining the spectrum. *Neurology* 89:1210–19

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