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# The State of the Art in the Genetic Analysis of the Epilepsies

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## Abstract

Genetic influences as causal factors in the epilepsies continue to be vigorously investigated, and we review several important studies of genes reported in 2006. To date, mutations in ion channel and neuroreceptor component genes have been reported in the small fraction of cases with clear Mendelian inheritance. These findings confirm that the so-called “channelopathies” are generally inherited as monogenic disorders. At the same time, the literature in common epilepsies abounds with reports of associations and reports of nonreplication of those association studies, primarily with channel genes. These contradictory reports can mostly be explained by confounding factors unique to genetic studies. The methodology of genetic studies and their common biases and confounding factors are also explained in this review. Amid the controversy, steady progress is being made on the epilepsies of complex inheritance, which represent the most common idiopathic epilepsy. Recent discoveries show that genes influencing the developmental assembly of neural circuits and neuronal metabolism may play a more prominent role in the common epilepsies than genes affecting membrane excitability and synaptic transmission.

## Introduction

The field of epilepsy genetics is contentious, particularly when it concerns the common epilepsies. More than a dozen loci have been suggested, the result of either linkage analysis and/or association analysis, but few of these findings have been replicated, let alone proven, and those that have are mostly for rare forms of epilepsy [1].

This report has two purposes. The first is to introduce the most common genetic analysis methods used in epilepsy studies and discuss their relative strengths and weaknesses. These methods are obscure to most epileptologists, but an appreciation of them is essential for understanding the literature. The second is to review selected epilepsy genetics publications from the past year. The intention of this article is to draw lessons from a number of illustrative examples, not to be a comprehensive review of the literature.

## Genetic Analysis Methods

Before genomic markers became available, twin and family studies were the main genetic methods. Today, the information from twin studies is dwarfed by molecular biologic methods, and family studies are now used less to determine mode of inheritance than to explore the familiality of the different traits in epilepsy syndromes. Linkage analysis is a method for localizing *major* effect genes to within several million base pairs. Linkage can be used either to test if a chromosomal region containing a suspected gene is related to disease expression, or to do a genome-wide search for disease-related loci. Association analysis can show that having a specific allele at a locus correlates with increased risk for disease. Mutation analysis looks for (usually exonic) sequence changes in specific genes to identify the disease gene.

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### How the methods have been used

Twin and family studies have been used to show that a genetic contribution to epilepsy exists.

**Linkage studies—**Most linkage studies in epilepsy have been conducted in single large pedigrees with many affected members, often searching for the gene over the whole genome. Linkage studies have also been used to prove or disprove the involvement of a specific gene (the "candidate") in disease expression. The most frequent etiologic assumption for choosing the candidate is that epilepsy is a "channelopathy"; thus, channel genes are frequent candidates. The alternative, an etiologicassumption–free approach using linkage, is the genome-wide screen either in a single large family with many affected family members or using many smaller families chosen because one or more family members has a specified form of epilepsy. However, few genome-wide studies using multiple families chosen for the presence of specific epilepsy syndromes have been undertaken [2-8].

**Association analyses—**Association analyses have mostly been used to assess whether the frequency of a particular allele (usually a single nucleotide polymorphism [SNP]) at a candidate gene differs between cases and controls. It may be used as part of a pure candidate gene approach, as a fine-mapping tool to follow-up linkage results, or in a hybrid design to examine candidates in a linked region. Association can be tested through a case-control or family-based design.

**Mutation analysis—**Mutation analysis looks for disease-related DNA sequence variants, usually in coding regions (exons), in candidate genes implicated by other approaches. If the disease-related mutation is in a non-coding region (eg, an intron or promoter region), studying only exons could lead to missing the susceptibility mutation, even if the gene being examined is the right one. Proving that a non-coding mutation is the sought-after mutation is often a difficult process.

## Strengths and Weaknesses of the Methods

### Twin studies

The starting point of twin studies is selecting the "pro-band" with the targeted phenotype. One examines both monozygotic (MZ) and dizygotic (DZ) pairs and compares concordance and discordance between MZ and DZ groups. As MZ pairs share all genes in common, discordance is usually attributed to environmental factors alone. In DZ pairs, who share, on average, half of their genes in common, the half not shared is viewed as the reason for discordance. It is a common belief that twin studies can be used to estimate the contribution of genetic and environmental causes of a disorder. In fact, twin pair analysis methods only apportion the variance in disease risk between three causal compartments: 1) shared genetic ($h^2$), 2) shared environmental ($c^2$), and 3) unique environment ($e^2$). One of the many assumptions of the method is that MZ and DZ twin pairs share exactly the same environment, an assumption that is often violated. Another assumption is that genetic components are independent of environmental components; in fact, the former may well influence the latter, and the components may also interact [9].

### Linkage analysis and the problem of heterogeneity

Linkage analysis works by looking for co-segregation of disease with marker alleles within families. A "linkage marker" is any known locus on the genome in which the alleles can be different in different people (ie, a polymorphic locus). Microsatellite loci (or short tandem repeats [STRs]) and groups of appropriately spaced SNPs are the usual markers for linkage [10].

Linkage has proven extremely successful for Mendelian diseases, but common diseases, like epilepsy, present problematic factors that can lead to failure to find true disease-influencing loci. The most problematic factors are heterogeneity and incorrect phenotype definition. These confounders affect both linkage and association analysis.

**Heterogeneity—**Heterogeneity exists when two or more traits cannot be distinguished clinically, so that families collected for genetic analysis will represent a mixture of the different diseases. With heterogeneity, a form of disease that is linked to a marker locus can become undetectable because the form(s) that are not linked may overwhelm the linkage or association evidence. The available linkage methods to take account of heterogeneity are useful but weak [11,12]. Association analysis lacks any such methods.

Heterogeneity can best be detected by stratifying the sample on clinical characteristics that enrich the data for one particular form of disease. For example, Durner et al. [13] initially found no evidence of linkage to adolescent-onset idiopathic generalized epilepsy (IGE) on chromosome 8. However, when juvenile myoclonic epilepsy (JME) families were removed, strong evidence of linkage emerged. This example also shows that linkage can validate new, etiology-based nosologic divisions.

**Phenotype definition—**An International League Against Epilepsy (ILAE)-defined clinical syndrome may not be an optimal phenotype for genetic study [14]. Clinical syndromes are often defined as a combination of age of onset, semiology, drug response, and other features, not all of which are necessarily related to genotype. The most conservative strategy is to define and strictly apply a phenotype that is as homogeneous as possible, a decision that involves a trade-off against increasing difficulty of patient recruitment. Unfortunately, this is seldom done. Looking for genes for IGE or febrile seizures can be justified but preferably in conjunction with pursuing more restricted and homogenous classifications. Using broad categories of epilepsy is akin to looking for “the cancer gene.”

Dividing the data in different ways can be helpful for developing hypotheses about the relationships between geno-types and phenotypes. For example, a chromosome 6 linkage signal for JME [15] was not seen in families identified through non-JME forms of IGE [16]. In another example, a genome scan of IGE families [17] tested hypotheses treating the syndromes JME, juvenile absence epilepsy (JAE), and epilepsy with generalized tonic-clonic seizures (EGTCS) as different phenotypes, yielding certain results. When the families were grouped according to seizure type (whether the patient or a family member had absence seizures) two linkage peaks, on 5p and 5q, appeared with nominally significant logarithm of odds scores not seen under the original phenotype definitions.

The advantage of linkage analysis is that finding strong evidence of linkage implies that the mapped locus is a major contributor to inherited disease etiology [18]. Linkage has the disadvantages that 1) it requires whole families to be most effective (meaning costly and difficult data collection) and 2) can seldom, by itself, identify the actual gene.

## Association analysis and how it differs from linkage analysis

The most important difference between the two methods is that linkage analysis detects co-inheritance within families of marker alleles with the disease. The specific identity of the marker alleles is irrelevant; the marker alleles co-segregating with disease will differ among families. In association analysis, one examines whether the patient population is more likely to have one particular allele at a locus than does the control population.

Linkage can be relatively insensitive to subtle effects on phenotype. Association analysis is highly sensitive and can detect an allele that has a secondary or tertiary effect on disease

expression. There are probably multiple genes that affect expression in minor ways but can still be detected by association analysis. As discussed in the following text, major genes may show no association at all.

In linkage analysis, the "region" in which that disease locus exists is often quite large: 2 million to perhaps 20 million base pairs. A significant association, on the other hand, demonstrates that the marker allele itself, or an allele of a "close by" gene, influences disease expression. The "region" is either the actual gene of the associated allele or a gene in the linkage disequilibrium region. The size of such regions, although quite variable, is often on the order of only tens of kilobases.

**Linkage disequilibrium and why ethnicity is important—**For association analysis to detect a gene, the disease allele must be in linkage disequilibrium (LD) with the marker allele. Finding disease-related genes by association (or LD mapping) is usually based on the assumption that a "founder effect" exists for the disease at that locus. That means when the disease susceptibility mutation first occurred, there was a distinctive allele at a marker locus (or, in the case of multiple SNPs, a distinctive pattern, or haplotype) that existed on the same strand of DNA as the mutation. The implication is that the mutation at the susceptibility locus happened only once. If the same disease mutation in a population happened multiple times, or there are other mutations at the disease locus leading to the same phenotype, then there will likely be no LD between a marker and the disease and there will be no association detectable. Thus, the population being studied is critical in association analysis.

For common diseases, multiple interacting loci probably cause disease, and these interactions likely differ in different populations. Disease allele frequencies can differ sharply in different ethnic groups. Thus, factors involving genetic background (ethnicity) can play a critical role in finding disease loci by association. For the common idiopathic epilepsies, there is a consensus that multiple genes are involved in their etiologies [19]. Because there are multiple pathways in biologic systems, it is virtually certain that multiple different genes can lead to similar disease phenotypes and there are likely to be different combinations of susceptibility genes in different populations. For example, the *EJM1* gene on chromosome 6p21 has been identified as the *BRD2* gene, which leads to one form of JME. The linkage appeared only in Caucasian families [20-22]. Later, Liu et al. [23] showed that a JME phenotype in a Central American population links to a 6p12 locus.

Thus, ethnicity must be taken into account when carrying out genetic studies. Not only does mixing populations increase heterogeneity, it also increases the chances of false-positive associations (population stratification).

## New Reports in Epilepsy Genetics in 2006

We review papers on six topics in genetic epilepsies: 1) the *BRD2* locus for JME on 6p21; 2) evidence for maternal inheritance in JME; 3) the *EFHC1* locus for JME on 6p12; 4) γ-aminobutyric acid (GABA) channel loci for IGE and childhood absence epilepsy (CAE); 5) calcium channel genes; and 6) a twin study of Rolandic epilepsy.

### JME and the *BRD2* gene

Lorenz et al. [24•] and Cavalleri et al. [25••] reported replication of an association of the *BRD2* gene with JME or electroencephalographic phenomena. A linkage on 6p21 to JME had been first linkage analysis reporting a locus for a common form of epilepsy [2]. The linkage had later been replicated in two other studies [20,26]. Pal et al. [21] had reported that the EJM1 locus in this linked region was *BRD2* (originally RING3).

Lorenz et al. [24•] replicated an association with *BRD2*, not directly with the JME phenotype but with the trait of photoparoxysmal response. Their sample consisted of 1) 111 IGE patients with varying IGE syndromes (eg, JME, JAE, CAE, EGTCS, and epilepsy with grand mal seizures on awakening [EGMA]); 2) 40 subjects with photoparoxysmal response only, and 3) 36 subjects with other seizure disorders. The authors suggest that the association is seen in both the IGE and non-IGE groups. Pinto et al. [8] performed a linkage scan for the photoparoxysmal phenotype and found evidence for genes on chromosomes 7q32 and 16p13. As discussed previously, linkage analysis and association analysis have different sensitivities, so the results of Pinto et al. [8] do not necessarily contradict those of Lorenz et al. [24•].

Cavalleri et al. [25••] tested the *JME-BRD2* association in five different populations: English, Irish, German, Australian, and Indian. They reported significant association of *BRD2* with JME in the English and Irish populations but not in the other three. The failure to see an association in the Indian population supports the earlier observation of Sander et al. [27] and Greenberg et al. [20] that the 6p21 locus appears restricted to Caucasian populations. In light of the report by Lorenz et al. [24•] using the same German data collection as that used in the Cavalleri et al. [25••] study, it is interesting that they did not show evidence of association. It is notable that Lorenz et al. [24•] apparently used a more restrictive phenotype than that used for the German data in the Cavalleri et al. [25••] report. The makeup of the Australian population is unclear.

## Maternal inheritance of JME

Pal et al. [28••] report that JME exhibits a parent-of-origin effect. Greenberg et al. [20] had reported evidence from linkage analysis that JME is maternally inherited at the 6p21 locus.

Pal et al. [28••] show that family data support maternal inheritance in JME. Interestingly, support is observed not only in the families that showed significant evidence of linkage on chromosome 6p21 but also in the group of families that rejected linkage at that locus, suggesting that the origins of the JME phenotype may be restricted to a portion of the brain whose development is controlled by imprinted genes [29]. There was no evidence for maternal transmission in the non-JME syndromes JAE and EGTCS, although the sample was small. There was also evidence of independent transmission of absence and myoclonic seizures, suggesting separate genetic influences. In addition, Pal et al. [28••] demonstrated a striking female preponderance among JME cases after correcting for ascertainment bias, amounting to a 12.5 relative risk for women.

## JME and the *EFHC1* gene

Suzuki et al. [30], Ma et al. [31], Pinto et al. [32], and Stogmann et al. [33] report evidence both for and against *EFHC1* being the JME susceptibility gene in the 6p12 region. Liu et al. [23] had originally reported linkage of JME to chromosome 6p12 in Central American families, a finding later supported by Pinto et al. [34]. Suzuki et al. [35••], using mutation analysis, asserted that the epilepsy gene in the linked region was *EFHC1*, after finding *EFHC1* mutations in six out of 44 probands.

Suzuki et al. [35••] looked for mutations in all the genes in a 3.5-cM (approximately $3.5\times10^6$ base pairs) *EFHC1*-containing region of 6p12. They concluded that only *EFHC1* could be the responsible gene. Previously, Suzuki et al. [35••] showed that different missense mutations segregated with disease in four families. Mutations were not seen in all the JME probands, leaving open the question whether non-coding polymorphisms could also be responsible. In the more recent work, they sequenced 14 other genes in the region and observed no mutations that co-segregated with disease. They previously observed that *EHFC1* mutations that were seen in four patients were not seen in more than 600 healthy, ethnically matched controls,

making the gene frequency for the mutations less than 0.001. The low gene frequency raises the following question: if JME is a common disease in the originating geographical region, can *EFHC1* or these mutations be a major cause of disease? (Note: These authors refer to the *6p12* gene as *EJM1*, although that designation was originally assigned to the locus at 6p21, and other publications have used, and continue to use, the original designation. Readers should be aware of the dual use.)

Stogmann et al. [33] sequenced *EFHC1* in 61 patients with IGE. (The original finding was in JME patients, not IGE in general.) They identified five "pathogenic" variants, that is, exonic mutations (it is unclear what "pathogenic" means) that they could not detect in 368 controls. One mutation was found in one of 372 patients with temporal lobe epilepsy (TLE). One problem is that the authors sequenced the gene in the IGE patients to find variants. They tested the controls and TLE patients for the specific variants they found in the IGE patients but it appears they did not sequence the gene in the controls or TLE patients. Thus, we do not know the overall distribution of variants that might be found in the controls/TLE patients and so cannot judge the importance of the identified variants to disease pathology, a criticism that can also be applied to other studies in the literature.

Pinto et al. [34] previously reported linkage evidence for a 6p12 locus in Dutch JME families and investigated *EFHC1* to look for mutations in those families. They found several variants of *EFHC1* in JME patients but none that segregated with the disease.

Ma et al. [31] also screened for *EFHC1* in JME patients. Although they found one family with a mutation that had been reported by Suzuki et al. [35••], it could not be determined if it segregated with the disease. Other polymorphisms showed no difference between cases and controls.

Thus, *EFHC1* is an interesting positional candidate but remains to be replicated.

## GABA receptor genes and IGE

Urak et al. [36], Hempelmann et al. [37], Chou et al. [38], Kinirons et al. [39], and Ma et al. [31] studied GABA receptor genes and their relation to IGE. Many antiseizure drugs interact with the GABA system; thus, mutations in GABA-related genes have been presumed candidates for epilepsy-susceptibility genes. GABA-related genes reported to be seizure-susceptibility genes include *GABRD*, *GABRA1*, *GABRB3*, and *GABRG2*. These have all been derived from studies of individual large families or a few smaller families. Results of different studies have been contradictory.

Following-up on a positive candidate gene–association study of *GABRB3* with CAE that was reported earlier by Feucht et al. [40], Urak et al. [36] screened 45 CAE patients from their earlier study for mutations in exons, intron-exon boundaries, and regulatory sequences of the gene. They found no functional mutations but located 13 additional polymorphic SNPs. Using these SNPs, they defined four haplotypes and found significant evidence of association using the transmission/disequilibrium test with the same 45 CAE subjects. They went on to show that the CAE-associated haplotype caused lowered transcriptional activity at the promoter that leads to reduced nuclear protein binding.

Hempelmann et al. [37] attempted to replicate the findings of Urak et al. [36], but they examined many more CAE patients than Urak et al. ($n = 250$) and also examined JME patients ($n = 303$), JAE patients ($n = 123$), and patients with awakening GTC seizures ($n = 104$) in addition to 559 controls. However, whereas Urak et al. [36] reported association with a haplotype defined by five SNPs, Hempelmann et al. [37] used only one of those SNPs (rs4906902), designating it a tagging SNP for Urak et al.'s haplotype 2. Hempelmann et al. [37] also designated rs4906902

as the “functional C-allele,” although Urak et al. [36] only suggested its possible role in functionality. Thus, because the experiments of Urak et al. [36] were not fully duplicated, it is unclear to what extent the work of Hempelmann et al. [37] is a failure to replicate the original findings.

Chou et al. [38] tested SNPs in the gamma-2 subunit of *GABRG2*, a gene identified in two different individual high-density families [41,42]. Chou et al. [38] examined two different SNPs in patients with IGE. For the first, an intronic SNP at nucleotide 3145, no difference was seen between cases and controls. In the second, rs211037, a statistically significant difference was found between cases and controls. It is important to emphasize that the 77 patients had a variety of IGE forms (including JME, JAE, CAE, EGTCS, as well as “overlap syndromes” and unclassified cases), and the sample was likely too small to report results by epilepsy syndrome.

Kinirons et al. [39] also examined a number of SNPs in the *GABRG2* receptor, including rs211037. These authors also examined IGE patients in a slightly larger sample ($n = 99$) than Chou et al. [38] ($n = 77$). They found no evidence of an association with the SNP examined by Chou et al. [38]. Kinirons et al. [39] also tested a variety of epilepsies for SNP associations. These epilepsies included symptomatic epilepsy, hippocampal sclerosis-caused epilepsy, and febrile seizures, among others. They used two cohorts (A and B) of patients with a number of different tagged SNPs, which theoretically also test association with distinctive haplotypes. In cohort A, two SNPs yielded positive evidence of association in the “symptomatic localization-related hippocampal sclerosis” group, a classification that might not be expected to yield evidence of a genetic influence. The most significant *P* value would barely survive a correction for the number of tests performed, a fact pointed out by the authors. However, none of the SNPs that yielded positive evidence of association in cohort A showed evidence of association in cohort B. The authors did not examine the IGEs by IGE syndrome. This study appears to be an intentional cautionary example with regard to association studies.

Ma et al. [31], in addition to testing *EFHC1*, also examined the *GABRA1* gene, reported to have a mutation leading to JME in a single family with autosomal dominant JME [43]. The families tested by Ma et al. [31] were chosen because they also appeared to show autosomal dominant transmission. Ma et al. [31] report finding no mutations in *GABRA1* in their 33 JME families.

## Calcium channel genes

Liang et al. [44] and Chioza et al. [45] examined the calcium channel gene *CACNA1H*. Chen et al. [46] had reported association with exon variants in the *CACNA1H* gene and CAE in the Chinese Han population, observing 12 missense mutations in 14 patients, mutations not observed in controls.

Liang et al. [44], drawing from the same population as Chen et al. [46], sequenced exons in 100 additional CAE trios and in 191 controls, finding 14 variants. Twelve of them were newly observed, but most were not confirmed or were even more frequent in CAE patients than in controls. One variant was found in normal controls but not in CAE trios, the significance of which is unclear. One SNP was found in 17 of 100 CAE patients but not in any of 191 controls. The various frequency observations would appear to constitute separate tests, which has an impact on the significance of any findings. It is difficult to evaluate the impact of finding one SNP in 17 of 100 patients and zero of 191 controls, especially as this SNP was not reported in the original study by Chen et al. [46]. As noted previously, a gene for a common disease would be predicted to show a notable frequency in the population, especially with the assumption of reduced penetrance.

Chioza et al. [45] tested *CACNA1H* in European CAE cases and controls. They found neither of the variants reported by Liang et al. [44] nor any association with CAE. However, because Chioza et al. [45] looked at Europeans and Liang et al. [44] looked at Han Chinese, one might not expect to see the same variants.

### A twin study of Rolandic epilepsy

Vadlamudi et al. [47] report no co-twin concordance for Rolandic epilepsy (RE) in twins, implying there is no genetic component to RE. Previous twin studies had showed evidence of a genetic contribution for both RE and centrotemporal sharp waves [48] and had indicated that 10% of relatives of RE patients have seizures [49]. Mendelian variants of RE are also known. Vadlamudi et al. [47] used four twin registries (Virginia, Norway, Denmark, and Australia) to study RE probands and co-twins, and concluded that inherited factors are not important in RE.

The study can be criticized because the methods used for ascertaining a history were too insensitive to detect the subtle seizures of RE, among other issues. For example, the prevalence of RE as a fraction of all epilepsies in the registries was not stated, but it was only 2% in one of the samples (a figure far lower than expected), and nine of the 10 MZ pairs were female [50]. These facts suggest not only a notable under-ascertainment of RE (RE usually constitutes 10%–15% of all epilepsies) [51,52], but a sex bias as well, because RE shows a 3:2 male preponderance [49]. Also, RE patients frequently have subtle symptoms (nocturnal facial tingling, drooling), and such symptoms may not be reported to parents and/or may not be interpreted as signifying seizure. The prevalence of RE was assessed by means of a postal questionnaire with the one question: “Do you have or have you had epilepsy? Loss of consciousness, other forms of jerks, twitches or convulsions in the arms or legs?”. This is unlikely to be a sensitive enough method of detection. These issues bring the validity of the findings and conclusions into question.

## Conclusions

These reports are typical of many of the published reports on epilepsy genetics over the past few years—reports of associations and linkages and failure to replicate associations and linkages are common (Table 1). Some of the papers in the literature have clear methodologic or statistical flaws. However, one theme stands out both this year and in other years: there is a concentration on particular genes, mostly channel genes, that were indicated either in studies of single families or because they fit the channelopathy paradigm for epilepsy, or both [53]. Some channel genes have been shown to be causative of some rare forms of epilepsy (eg, the sodium channel gene *SCNA1* and severe myoclonic epilepsy of infancy [54] and benign familial neonatal convulsions and the potassium channel genes *KCNQ2* and *KCNQ3*[55]), but few others have been proven and none has been shown to play any role in common varieties of IGE. Interestingly, few genes have been identified through linkage scans of collections of families chosen through distinct phenotypes, and of those that have, only *BRD2* has been replicated, but it is not a channel gene. The identification of cystatin B, a protease inhibitor, as the cause of progressive myoclonus epilepsy of Unverricht-Lundborg (OMIM 254800) [56] should give us pause before we accept as standard belief that all epilepsies are channelopathies. An early candidate for the progressive myoclonus epilepsy gene on 21q23 was *EHOC-1* because it had “channel-like” domains that the true gene does not have [57]. *BRD2*, if it is unequivocally demonstrated to be *EJM1*, will be another example of a non-channel gene involved in common epilepsy. Furthermore, cystatin B, *BRD2*, and *EFHC1* may all influence apoptosis and may produce susceptibility to epilepsy by affecting brain development. We do not know enough about IGE to be able to depend on a presumed etiology to lead us to the causative genes. One can argue that the single-minded belief in a presumed etiology has led to contention in the field and much wasted effort.

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**Table 1**

Summary of recent genetic studies in epilepsy

| Syndrome | Gene | Type of study | Original finding | Follow-up finding | Study |
|---|---|---|---|---|---|
| JME | *BRD2* | Association analysis | Markers in *BRD2* associated with Caucasian JME patients | | Greenberg et al. [20], Pal et al. [21] |
| | | Association analysis | | *BRD2* associated with photoparoxysmal response in a German population with mixed IGE-related phenotypes | Lorenz et al. [53] |
| | | Association analysis | | *BRD2* found associated with JME in English and Irish population samples, but not in Indian, German, or Australian | Cavalleri et al. [25••] |
| | | Linkage analysis | Linkage data suggested imprinting in *EJM1* gene (later shown to be *BRD2*) at 6p21 | | Greenberg et al. [20] |
| | | Population-based analysis of family affectedness data | | Supports maternal inheritance of JME as well as increased female risk for JME | Pal et al. [28••] |
| | *EFHC1* | Mutation analysis | Mutations found in *EFHC1* that segregate with disease in 5 of 44 families | | Suzuki et al. [35••] |
| | | Mutation analysis | | No mutations segregating with disease found in other genes in the linkage region, supporting *EFHC1's* involvment in JME in this population. | Suzuki et al. [30] |
| | | Mutation analysis | | Found 5 mutations in *EFHC1* in 61 IGE patients; mutations not seen in controls but meaning unclear | Stogmann et al. [33] |
| | | Mutation analysis | | Found variants of *EFHC1* in population supporting linkage to the region but none that segregated with disease in families | Pinto et al. [32] |
| | | Mutation/ association analysis | | No difference in cases and controls in *EFHC1* coding polymorphisms | Ma et al. [31] |
| CAE | GABA receptor genes *GABRA1, GABRG2, GABRB3* | | Reported in studies of single large families and association study | | Baulac et al. [41], Wallace et al. [42], Feucht et al. [40, Cossette et al. [43] |
| | *GABRB3* | Association analysis | | Found association with haplotypes in 45 CAE subjects | Urak et al. [36] |
| | *GABRB3* | Association analysis | | Attempted to replicate Urak et al. [36] with larger sample and different IGEs but found no association | Hempelmann et al. [37] |
| | *GABRG2* | Association analysis | | Tested SNPs in gene identified from linkage; no association but IGE type mixed | Chou et al. [38] |
| | *GABRG2* | Association analysis | | Tested SNP association in several different forms of epilepsy; no association found | Kinirons et al. [39] |
| JME | *GABRA1* | Linkage analysis | Linked to JME in a single large family | | Cossette et al. [43] |
| | | Mutation analysis | | Tested gene using 33 JME families similar to original; no mutations found | Ma et al. [31] |
| CAE | Calcium channel gene *CACNA1H* | Mutation analysis | Association with exon variants in CAE in Chinese Han population | | Chen et al. [46] |
| | | Mutation analysis | | Found no variants nor any association (but this was in a European population, not Chinese) | Chioza et al. [45] |
| | | Mutation analysis | | Found 14 variants in 100 CAE patients (Chinese populations); significance unclear | Liang et al. [44] |
| Rolandic epilepsy | | Twin study | Samples from 4 twin registries showed no evidence of increased concordance, | | Vadlamudi et al. [47] |

| Syndrome | Gene | Type of study | Original finding | Follow-up finding | Study |
|---|---|---|---|---|---|
| | | | suggesting no genetic component; study confounded by incomplete data collection and questionable sampling | | |

CAE—childhood absence epilepsy; GABA—gamma-aminobutyric acid; IGE—idiopathic generalized epilepsy; JME—juvenile myoclonic epilepsy; SNP—single nucleotide polymorphism.