EEG of asymptomatic first-degree relatives of patients with juvenile myoclonic, childhood absence and rolandic epilepsy: a systematic review and meta-analysis

Mariam Tashkandi [1], Duaa Baarma [2], Andrea C. Tricco [3], Cyrus Boelman [1], Reem Alkhater [4], Berge A. Minassian [1,5]

[1] Program in Genetics and Genome Biology, The Hospital for Sick Children, Institute of Medical Science, University of Toronto, Toronto
[2] Paediatric Neurology Division, Department of Paediatrics, King Abdullah Specialist Children Hospital, Riyadh
[3] Knowledge translation program, Li Ka Shing Knowledge Institute of St Michael's hospital, Epidemiology division, Dalla Lana school of public health, University of Toronto, Canada
[4] Johns' Hopkins Aramco Healthcare, Dhahran, Saudi Arabia
[5] Division of Neurology, Department of Pediatrics, University of Texas Southwestern, Dallas, USA

Correspondence:
Berge Minassian
University of Texas Southwestern
Medical Center,
5323 Harry Hines Blvd.,
Dallas TX 75390,
USA
<berge.minassian@utsouthwestern.edu>

ABSTRACT – *Aims.* Rolandic (RE), childhood absence (CAE) and juvenile myoclonic (JME) epilepsy encompass centrotemporal sharp waves, 3-Hz spike waves and >3-Hz spike or polyspike waves, respectively. Evidence abounds for genetic roles in all three syndromes, yet involved genes for the vast majority of patients remain unknown. It has long been proposed that while each disease is genetically complex, its specific EEG trait may represent a genetically simpler endophenotype. This meta-analysis of the literature focuses on the frequency of EEG traits in clinically unaffected first-degree relatives towards determining inheritance patterns of the EEG endophenotypes.
Methods. We used the Preferred Reporting Items for Systematic Review and Meta-Analysis for protocols (PRISMA-P) and searched Medline, EMBASE, CINHAL and the Cochrane Central Register of Controlled Trials.
Results. Following extensive screening, 15 studies were included with a total of 3,858 asymptomatic relatives. The prevalence of 'abnormal' EEG waves was 21%, 42% and 33% for JME, CAE and RE, respectively, close to what would be expected based on Mendelian inheritance.

However, breaking down the reported EEG abnormalities, most consisted not of the respective EEG signature traits -prevalences of which were as low as 5%- but of non-specific EEG 'abnormalities'/variants.

Conclusions. Prevalence of non-specific EEG 'abnormalities'/variants in the general population ranges from 0.1 to 10%. Underlying this 100-fold-wide range is a spectrum of what is considered 'abnormal' or variant. The prevalences of 'abnormalities'/variants in asymptomatic siblings in RE, CAE and JME significantly exceed even the highest value in the general population and fall within Mendelian expectations. These results suggest that EEG 'abnormalities'/variants shared with the general population are enriched in the three syndromes and are endophenotypes inherited in a genetically simple near-Mendelian fashion. Future work with modern EEG variant definitions should uncover genetic variants contributing to neuronal hypersynchrony in epilepsy.

Key words: Rolandic epilepsy, childhood absence epilepsy, juvenile myoclonic epilepsy, endophenotype, EEG trait, spike wave, sibling, unaffected

The three most common childhood epilepsies are Rolandic (RE), childhood absence (CAE) and juvenile myoclonic (JME) epilepsy, accounting for 15%, 10-15% and 5-10% of cases, respectively (Avanzini and Noebels, 2009; Panayiotopoulos, 2010; Berg and Millichap, 2013; Camfield *et al.*, 2013; Pal *et al.*, 2016; Verrotti *et al.*, 2017). There is abundant evidence that genetic factors play important roles in each of these conditions though none (in the vast majority of families) is inherited in a Mendelian fashion, and all three are therefore genetically complex (Anderman and Metrakos, 1969; Delgado-Escueta, 2007; Panayiotopoulos, 2010; Panayiotopoulos *et al.*, 2012). Despite the genetic and genomic revolutions of the last three decades, only a few genes have been associated with these very common diseases, and then only in a small minority of patients.

The genetic complexities of CAE and JME were already recognized even prior to the two being carved out of what was called in the early 1950s, 'centrencephalic' epilepsy (Penfield, 1952). In their seminal work, Metrakos and Metrakos (1961a) reported that approximately 50% of clinically unaffected, age-matched first-degree relatives of patients with centrencephalic epilepsy had the same age-dependent generalized EEG abnormalities as the latter, and suggested that while the epilepsy itself was not inherited in a Mendelian fashion, the EEG trait, present as it is in nearly 50% of young adolescent relatives, may well be (Metrakos and Metrakos, 1961a). Following the spinoff of CAE and JME from the parent 'centrencephalic' concept, EEG studies of relatives of these patients continued to be carried out, but results usually showed rates substantially lower than 50%.

A decade following the work of Metrakos and Metrakos, studies in RE also reported a rate of EEG abnormality in clinically unaffected siblings of approximately 50% when the siblings were studied during the range of childhood years in which RE occurs (Bray and Wiser, 1964; Heijbel *et al.*, 1975). More recent work, however, questioned the role of genes in RE, based on the rate of non-concordance for the clinical syndrome in monozygotic twins (Valdamudi *et al.*, 2006). Meanwhile, ongoing EEG studies of relatives of RE patients continued to show rates of EEG abnormalities substantially higher than in children in the general population. RE, CAE and JME are not only common, they also are 'pure' epilepsies in which the CNS is otherwise grossly morphologically and functionally intact. As such, understanding the pathogeneses of these benign conditions will be highly insightful to the overall understanding of epilepsy. Solving the genetic complexities of RE, CAE and JME would be greatly aided if any aspect of these conditions, *e.g.* their specific EEG traits, were endophenotypes inherited in simpler, perhaps a Mendelian, fashion. Given the opaqueness of, and contradictions in the literature regarding, the frequencies of EEG abnormalities in unaffected relatives of patients with RE, CAE and JME, we conducted a systematic review and meta-analysis of this literature to clarify the current state of knowledge. It is hoped that this work will serve as a basis and springboard for additional studies that will resolve the genetics of the epileptiform abnormalities underlying RE, CAE and JME.

Methods

Protocol

A protocol was developed using the Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols (PRISMA-P) (Moher *et al.*, 2015) and registered with the PROSPERO database (CRD42013005615).

Eligibility criteria

We included studies using cohort, case-control or cross-sectional methodology examining EEG in asymptomatic relatives (parents, siblings or offspring) of epileptic patients of all ages. Both English and non-English language, published and unpublished, reports were included.

Search

Medline, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials were searched on July 5, 2013. Searches were performed with no year or language restrictions, using the Medical Subject Headings and text words and phrases: Juvenile myoclonic epilepsy, Janz syndrome, idiopathic epilepsy, genetic epilepsy, electroencephalograph, humans, childhood absence epilepsy, pyknolepsy, idiopathic generalized epilepsy, centrencephalic epilepsy, Rolandic epilepsy, benign childhood epilepsy with centrotemporal spikes, epilepsy syndrome, and Sylvian seizures. Appropriate wildcards were used to account for plurals and spelling variations. This search was conducted by an experienced librarian and peer-reviewed by another librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist (McGowan *et al.*, 2010). The electronic search was supplemented by scanning the reference lists of included studies and relevant reviews. The full search strategy for MEDLINE can be found in the *supplementary material* and the others are available upon reasonable request from the corresponding author.

Study selection

A pilot test was conducted on a random sample of 25 titles and abstract citations. After 94% agreement was achieved, two reviewers (MT and DB) independently screened the search results for inclusion. We obtained the full-text of potentially relevant articles and assessed them in a similar manner. Discrepancies were resolved by discussion with a third reviewer (BAM).

Data collection process

After a pilot test of 25 articles, two independent reviewers (MT and DB) performed data extraction on all the selected articles using the standardized data extraction form. To ensure accuracy, the reviewers extracted all data in duplicate and conflicts were resolved through discussion amongst the team. When multiple publications reported data from the same population (companion reports), we considered the study with the largest sample size as the major publication, and used the other report(s) for *supplementary material* only.

Methodological quality

We assessed methodological quality of individual studies using the Newcastle-Ottawa Scale (NOS) (Wells *et al.*, 2014), which consists of eight items pertaining to selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that outcome of interest was not present at start of study), comparability (comparability of cohorts on the basis of the design or analysis), and outcome (assessment of outcome, sufficient duration of follow-up, adequacy of follow-up). We modified the NOS for cross-sectional studies to include the following five items: representativeness of the exposed cohort, ascertainment of exposure, comparability of cohorts on the basis of the design or analysis, assessment of outcome, adequacy of response rate (Higgins and Thompson, 2002; Fnais *et al.*, 2014; Wells *et al.*, 2014).

Synthesis of results

We described the results narratively and conducted a meta-analysis using a random effects model, as statistical heterogeneity was expected across the studies. For the meta-analysis, we combined the extracted data from the studies to calculate a pooled estimate of the proportion of abnormal EEG in each population along with the corresponding 95% confidence interval (CI) based on a normal distribution (Higgins and Thompson, 2002). We assessed statistical heterogeneity using the I^2 statistic and depicted the studies in a forest plot to examine heterogeneity visually. All analyses were conducted using the R statistical program (R Development Core Team 2010) with the metafor package (Viechtbauer, 2010).

Results

Study selection and study characteristics

The literature search yielded 10,223 citations. After excluding 255 duplicates, 9,968 studies were screened for eligibility. A total of 211 potentially relevant full-text articles met a preliminary screen for epilepsy, EEG examinations, and mention of relatives. From these, 191 were excluded because they clearly did not include asymptomatic relatives (86), did not study the epilepsies in question or their EEGs (77), did not provide primary data (10), or were only abstracts or could not be located (18). A total of 15 studies remained. These had been conducted in Germany (Tsuboi and Christian, 1973; Doose *et al.*, 1973; Degen and Degen, 1992; Wandschneider *et al.*, 2010), the United States (Alonso *et al.*, 2005a, 2005b; Bali *et al.*, 2007), Turkey (Atakli *et al.*, 1999; Akgun *et al.*, 2009), Italy (Serra *et al.*, 2001;

Verrotti *et al.*, 2013), India (Jayalakshmi *et al.*, 2006), Sweden (Heijbel *et al.*, 1975), and Canada (Metrakos and Metrakos, 1961a) and published between 1961 and 2013. EEG recording times ranged from 20 to 60 minutes with varying capture of sleep.

Of the 15 studies, 11 were included in the meta-analysis. The design of two studies by Alonso and colleagues (cohort) differed from all the others (cross-sectional) and thus could not be combined with the others in the meta-analysis. Their results are nevertheless shown (*table 1*), as they represent valuable relevant data. The two other studies not included in the meta-analysis are those of Metrakos and Metrakos (1961a) and Tsuboi and Christian (1973) (*table 1*), both of which did not formally specify that the relatives studied were asymptomatic. However, this information was gleaned from details in their papers, including their selection of any-comer (and not multiplex) patients, and the sheer number of families and relatives studied. The vast majority of these families and relatives, given what we know of these epilepsies, would be expected to be asymptomatic. As such, we conducted a sensitivity analysis including these two studies in the meta-analysis, in addition to the 11 studies that were previously combined.

Juvenile Myoclonic Epilepsy

Six studies specified that their epileptic patients had JME and reported on EEG abnormalities in the patients and their relatives (Tsuboi and Christian, 1973; Atakli *et al.*, 1999; Alonso *et al.*, 2005a; Jayalakshmi *et al.*, 2006; Akgun *et al.*, 2009; Wandschneider *et al.*, 2010). Two of these studies were not included in the meta-analysis. One (Alonso *et al.*, 2005a) was not included because it differed in design (cohort) from the other studies (cross-sectional). This study also did not specify the degree of relatedness between relatives and patients. Notwithstanding, the results of this study are tabulated: there were 186 JME patients and 1,756 relatives, of whom 24 (1%) had EEG findings that were considered abnormal. These abnormalities were: generalized >3-Hz spike or polyspikes and waves (SPSW) in 15 subjects, 3-Hz spike waves (SW) in three, bursts of focal or diffuse slowing in four, and bursts of focal or diffuse sharp waves in two (*table 1*). The study by Tsuboi *et al.* was the other JME study not included in the meta-analysis, because it did not specify whether the relatives studied were clinically affected or not. There were 136 JME patients and 370 first-degree relatives of whom 262 (*i.e.* 71%) had EEG findings that were considered potentially abnormal. These were SPSW in 57 relatives and paroxysmal sharp waves in the remaining 205 (*table 1*).

The remaining four JME studies were all cross-sectional and specified the relatives as first-degree and unaffected (Atakli *et al.*, 1999; Jayalakshmi *et al.*, 2006;

Akgun *et al.*, 2009; Wandschneier *et al.*, 2010). There was a total of 108 JME patients in these studies and 206 first-degree relatives, of whom 39 (19%) had EEG abnormalities. These were SPSW in 18, 'theta waves' or intermittent generalized or paroxysmal slowing in 13, photoparoxysmal response (PPR) in three, centrotemporal spikes in three, bifrontal sharp waves in one, and single spikes in one (*table 1*).

Childhood Absence Epilepsy

Four studies looked at CAE (Metrakos and Metrakos, 1961b; Doose *et al.*, 1973; Degen and Degen, 1990a; Alonso *et al.*, 2005b). Two (Metrakos and Metrakos, 1961b; Alonso *et al.*, 2005b) were not included in the meta-analysis. The Metrakos and Metrakos (1961b) study did not specify the affected status of the relatives. The patients had 'centrencephalic' epilepsy, and were likely to be predominantly a mix of CAE and JME cases. There were 211 patients and 418 relatives. Of the latter, 145 had EEG abnormalities (35%), seven 3-Hz SW, and 138 with an unspecified mix of what were considered abnormalities (*table 1*). The study by Alonso *et al.* (2005b) was not included in the meta-analysis because of its different (cohort) design from the other studies (cross-sectional). In addition, their CAE cases were ones that evolved into JME and thus diverge from the common remitting CAE phenotype. There were 45 patients and 541 relatives of whom 38 (7%) had EEG abnormalities, which included three SPSW, 15 3-Hz SW, and the remainder, a mix of slow waves and isolated generalized or focal spikes (*table 1*).

The remaining two studies (Doose *et al.*, 1973; Degen and Degen, 1990a) were included in the meta-analysis and together encompassed 274 patients and 292 siblings of whom 104 (36%) were considered to have EEG abnormalities. Of these abnormalities, only 12 were 3-Hz SW and the remainder were a mix of runs of focal or generalized slow waves or sharp waves or spikes (*table 1*).

Rolandic Epilepsy

Five RE studies (Heijbel *et al.*, 1975; Degen and Degen, 1990b; Serra *et al.*, 2001; Bali *et al.*, 2007; Verrotti *et al.*, 2013) reported on EEG in unaffected relatives. All could be included in the meta-analysis. Overall, 275 relatives were studied of whom 82 (30%) had EEG abnormalities (*table 1*).

Meta-analysis

Eleven studies (Doose *et al.*, 1973; Heijbel *et al.*, 1975; Degen and Degen, 1990a; Degen and Degen, 1990b; Atakli *et al.*, 1999; Serra *et al.*, 2001; Jayalakshmi *et al.*, 2006; Bali *et al.*, 2007; Akgun *et al.*, 2009; Wandschneider

Table 1. Numbers and characteristics of abnormal EEGs in relatives of patients with JME, CAE and RE.

Author	Epilepsy	Number of patients	Average age of patients	Number of relatives studied*	Average age of relatives	Number and percent of relatives with abnormal EEGs	Number of relatives with SPSW	Number of relatives with 3-Hz SW	Number of relatives with CTS	Number of relatives with runs of focal or generalized slow waves 'theta waves'	Number of relatives with focal or generalized sharp waves or spikes
Alonso *et al.*, 2005a	JME	186	25.9	1756 (relatedness NS)	NS	24 (1%)	15 (1%)	3 (0.17%)	-	4 (0.22%)	2 (0.11%)
Atakli *et al.*, 1999	JME	37	20.33	48 (siblings)	24.17	13 (27%)	10 (20%) (5 PSW and 5 single-spike-wave)	-	3 (6%)	-	-
Akgun *et al.*, 2009	JME	21	23.9	21 (siblings)	22.8	7 (33%)	1 (5%)	-	-	6 (29%)	-
Jayalakshmi *et al.,* 2006	JME	31	22	116 (1st degree NOS)	31.1	15 (13%)	9 (8%) (2 of which were photoparoxysmal)	-	-	6 (5%)	-
Tsuboi and Christian, 1973	JME	136	NS	370 128 (siblings) 128 (parents) 114 (offspring) Relatives' affected status NS	NS	262 (71%) Siblings (n=87) (68%) Parents (n=73) (57%) Offspring (n=102) (89%)	57 (15%) Siblings (n=17) (13%) Parents (n=12) (9%) Offspring (n=28) (25%)	-	-	-	205 (55%) Siblings (n=70) (54%) Parents (n=61) (48%) Offspring (n=74) (65%)
Wandschneider *et al.*, 2010	JME	19	25.5	21 (siblings)	25.1	4 (19%)	1 (5%) photoparoxysmal 1 (5%) bifrontal sharp waves rather than strictly SPSW	-	-	1 (5%)	1 (5%)

Table 1. Numbers and characteristics of abnormal EEGs in relatives of patients with JME, CAE and RE (*Continued*).

Author	Epilepsy	Number of patients	Average age of patients	Number of relatives studied*	Average age of relatives	Number and percent of relatives with abnormal EEGs	Number of relatives with SPSW	Number of relatives with 3-Hz SW	Number of relatives with CTS	Number of relatives with runs of focal or generalized slow waves 'theta waves'	Number of relatives with focal or generalized sharp waves or spikes
Metrakos and Metrakos, 1961a	Centrencephalic epilepsy (likely a combination of CAE and JME)	211	NS	418 223 (siblings) 195 (parents) Relatives' affected status NS	NS	145 (35%) Siblings (*n*=119) (53%) Parents (*n*=26) (13%)	-	7 (2%) Siblings (*n*=5) (2%) Parents (*n*=2) (1%)	-	138 (33%) (NS mix of focal or generalized slow waves or sharps or spikes) Siblings (*n*=114) (51%) Parents (*n*= 24) (12%)	-
Alonso et al., 2005b	CAE evolving to JME	45	6.9	541 (relatedness NS)	NS	38 (7%)	3 (0.55%)	15 (3%)	-	9 (2%)	11 (2%)
Degen and Degen, 1990a	CAE	22	NS	50 (siblings)	NS	36 (72%)	-	-	-	36 (72%) (NS mix of focal or generalized slow waves or sharps or spikes)	-
Doose et al., 1973	CAE	252	NS	242 (siblings)	NS	68 (28%)	-	12 (5%)	-	56 (23%) (specified [see reference] mix of EEGs considered abnormal due to runs of slow 'theta' waves with or without additional presence of spikes)	-
Bali et al., 2007	RE	23	NS	30 (siblings)	10.3	13 (43%)	-	2 (7%) (these two also had CTS)	13 (43%)	-	-
Degen and Degen, 1990b	RE	43	NS	64 (siblings)	NS	24 (38%)	-	-	2 (3%)	21 (33%) (the abnormality in these 21 is described as mainly hypnagogic or hypnapompic 2.5-4-Hz generalized spikes One child had both typical CTS and this abnormality)	-

Table 1. Numbers and characteristics of abnormal EEGs in relatives of patients with JME, CAE and RE (*Continued*).

Author	Epilepsy	Number of patients	Average age of patients	Number of relatives studied*	Average age of relatives	Number and percent of relatives with abnormal EEGs	Number of relatives with SPSW	Number of relatives with 3-Hz SW	Number of relatives with CTS	Number of relatives with runs of focal or generalized slow waves 'theta waves'	Number of relatives with focal or generalized sharp waves or spikes
Verrotti et al., 2013	RE	9	7.8	8 (siblings)	7.7	2 (25%)	-	-	2 (25%)	-	-
Serra et al., 2001	RE	0	NS	114 41 (siblings) 73 (parents)	Siblings 2-16 Parents NS	31 (27%) Siblings (n=14) (34%) Parents (n=17) (23%)	-	-	14 (34% (all siblings)	17 (23%) (all parents; specific description: sharp 'theta' waves, uni- or bilateral)	-
Heijbel et al., 1975	RE	19	9.1	59 27 (siblings) 32 (parents)	Siblings 10.3 Parents NS	12 (20%) Siblings (n=6) (22%) Parents (n=6) (18%)	-	-	7 (12%) Siblings (n=6) (22%) Parents (n=1) (3%)	5 (15%) (all parents)	-

*Relatives are unaffected siblings except where indicated; JME: juvenile myoclonic epilepsy, CAE: childhood absence epilepsy, NS: not specified, NOS: not otherwise specified; SPSW: generalized >3-Hz spike or polyspike-and-slow waves, 3-Hz SW: 3-Hz spike-and-slow waves, CTS: centrotemporal sharp or spike waves.

et al., 2010; Verrotti *et al.*, 2013) were included in the meta-analysis. The pooled prevalence of abnormal EEG in asymptomatic relatives of patients with JME, CAE and RE was 30.51% (95% CI: 20.70, 40.33; I^2=87.9%). Separating according to epilepsy syndromes showed the highest prevalence in CAE (41.82%), followed by RE (30.42%) and JME (21.10%). Grouping based on asymptomatic siblings only (*i.e.* excluding other relatives), the overall prevalence was 34.76% (95% CI: 24.79, 44.73; I^2=79.61%), and by syndromes: CAE 41.8%, RE 33.76%, and JME 26.57% (*tabulated and detailed in supplementary table 1 and figure 1*).

Grouping according to characteristic EEG abnormalities (SPSW, 3-Hz SW or CTS) or 'other', the pooled prevalences in asymptomatic relatives were: SPSW 7.14%, 3-Hz SW 5.40%, CTS 14.39%, 'other' waves 23.56%, and PPR 9.04%. Restricting to siblings alone: SPSW 7.74%, 3-Hz SW 5.40%, CTS 25.55%, and PPR 14.13% (*supplementary table 2 and figures 2-5*).

Sensitivity analysis

The sensitivity analysis included the 11 studies as well as the results reported in the large Metrakos and Metrakos (1961a) and Tsuboi and Christian (1973) studies. The pooled prevalence of abnormal EEG in asymptomatic relatives was 37.15% (95% CI: 25.53, 48.76; I^2=95.03%). In this case, the highest prevalence was in relatives of patients with JME (42.41%) followed by CAE (38.43%), and RE (28.55%). When only siblings were considered, the pooled prevalence was 41.80% (95% CI: 31.24, 52.35; I^2=88.78%), divided between siblings of JME (43.66%), RE (33.76%), and CAE (46.41%) (*supplementary figure 6*).

The pooled prevalence for SPSW was 10.97%, for 3-Hz SW 3.57%, and CTS 14.39%. The pooled prevalence for 'other' abnormalities was 31% and for PPR 9.04%. Considering only siblings, the pooled prevalences were SPSW 10.97%, 3-Hz SW 4.09%, CTS 25.55%, and PPR 14.13% (*supplementary figures 7-10*). Finally, the pooled prevalence of abnormal EEG in parents was 28.79%.

Quality of included studies

The quality of the included studies is provided in the *supplementary material*. More than 50% of the included studies failed to ascertain exposure adequately.

Discussion

The 15 studies reviewed in this work comprised a total of 4,912 subjects including 1,054 epileptic patients and 3,858 relatives; large numbers that would be difficult to obtain in any one independent study. The highest percentages of 'abnormal' EEG in asymptomatic relatives are obtained by combining all 15 studies (sensitivity analysis) and focusing on siblings alone, which is important given the age dependency of the syndromes studied. The pooled number in that case is 42% distributed as 44% for JME, 34% for RE, and 47% for CAE. Accounting for missed abnormalities due to the short length of routine EEGs, the numbers are sufficiently close to 50% to suggest that EEG abnormalities in these common syndromes are autosomal dominant traits, as proposed by the authors of the earliest and largest studies (Metrakos and Metrakos, 1961a; Doose *et al.*, 1973; Tsuboi and Christian, 1973; Heijbel *et al.*, 1975). If these syndromes indeed include dominant Mendelian contributions to their EEG endophenotypes, the locus could possibly be shared across two (*e.g.* JME and CAE) or more of the syndromes, or be different in each. But even in the latter case, if each of JME, CAE and RE has an underlying dominant locus, it would be surprising that the mutations in these loci have not come to light in the current genomic era, in which many hundreds of these patients have had whole-exome or genome sequencing. It is possible that these loci are in yet to be clarified non-coding genomic regions, or that in each case, there is wide genetic heterogeneity with numerous loci separately acting as a dominant predisposition for the EEG trait in separate families.

However, when certain studies are excluded, the numbers change. For JME, if one excludes the large Tsuboi and Christian (1973) study (506 subjects) on the grounds that the authors never quite specified whether the relatives were clinically affected or not, the prevalence of EEG 'abnormality' drops to close to 27%. Such a number, close to 25%, might suggest that the EEG endophenotype of JME is an autosomal recessive trait (or a series of separate recessive traits in different families). But if one looks closely at what is meant by EEG abnormalities in the different studies, the picture becomes even blurrier. For JME, in the Atakli *et al.* (1999) study, 20% of siblings (10 of 48 siblings studied) had SPSW, a number that approaches the overall ~25% figure. However, in the Akgun *et al.* (2009) study, the percentage for SPSW was only 5% (one of 21 siblings studied), while another 29% of siblings had 'theta' waves (*table 1*). What are the latter? They are bursts of slowing that are not quite epileptiform (*i.e.* lack spikes), but are unexpected enough to have been labelled as an abnormality, or potential abnormality. This raises a major question. To what extent are such irregularities, which in the present age, for clinical purposes, would not be considered epileptiform actual subtle endophenotypes of potential relevance towards understanding the genetic underpinnings of JME?

The above issues are even more pronounced in CAE. Here, the meta-analysis provides a figure of 42% and the sensitivity analysis 46%. However, if one looks at the numbers of siblings of CAE patients who have 3-Hz SW, it is no more than 5%, the remainder of the percentage being made up of 'theta' waves and other non-specific abnormalities/irregularities (*table 1*). Again, to what extent the latter constitute incomplete parts of the syndrome remains unknown. The situation is slightly clearer in RE. The percentages of EEG abnormalities in unaffected siblings in the five RE studies range from 22 to 43% (*table 1*). In some studies, the entire percentage is composed of the syndrome-specific CTS trait, while in the others, substantial portions of the percentages are derived from non-specific abnormalities such as 'theta' waves and generalized sharp waves (*table 1*). In the large Degen and Degen (1990b) study (64 siblings studied), the vast majority of abnormalities are hypnagogic or hypnapompic 2.5-4-Hz generalized spikes. This abnormality is not commonly discussed in RE, especially in clinical practice, where the CTS is considered the defining feature. However, it has been reported as a particularity of RE by other authors. Not all the RE studies reviewed in the present paper included sleep EEG recording, and none performed overnight EEGs. As such, it is likely that the percentages of CTS or abnormalities related to progression into or out of sleep are underestimated, suggesting a high EEG endophenotype(s) heritability in RE.

The reported incidence of EEG abnormalities in the general non-epileptic population varies drastically from les than 0·1% to 10% (Gibbs *et al.*, 1943; Cavazzuti *et al.*, 1980). This 100-fold range is emblematic of the same issue as in the above studies of epileptic relatives, namely of the question as to what is meant by 'abnormal'. Is uncommon 'abnormal', and by what fold should the frequency of a finding be higher in epileptic versus non-epileptic families to be considered 'abnormal'? Clearly, the EEG in epileptic families is substantially 'different' to that in the general population, with rates of 'abnormality' ranging from ~25 to 50% in the former versus a maximum of 10% in the latter, and therefore there is important information on the genetics of epilepsy within the EEG. A trait occurring at a frequency of 25% in siblings would likely be considered to be inherited in an autosomal recessive manner, and at 50% in an autosomal dominant, Mendelian manner. It is possible that 'defects' in a single gene inherited in a recessive or dominant fashion underlie the constellation of EEG 'abnormalities' in each of the above epilepsies (*i.e.* one gene for RE-associated EEG 'abnormalities' and one each for JME and CAE related-'abnormalities'). It is also possible that defects in any number of single genes underlie the set of 'abnormalities' associated with each syndrome (in other words, that the EEG trait is inherited in a Mendelian fashion but with genetic heterogeneity, *i.e.* different JME families with, for example, segregating 'defects' in different single genes). Another possibility is that variants in different genes underlie different EEG 'abnormalities'. Yet another is that variants in multiple genes summate to result in a range of 'abnormality' from simply 'uncommon' features (*e.g.* 'theta waves') to frank epileptiform spike waves. However, it is important to note that a multiplicity of genes involved cannot be very large, because otherwise rates in the 'Mendelian' range of ~25 to 50% would not be observed.

Clearly, much work lies ahead, but the genetic tools that were not available in the previous century of EEG, now are. Future studies should carefully describe and correlate EEG irregularities of age-appropriate relatives of epileptic patients with their genome sequences. JME, CAE and RE families are highly likely to yield a relatively small number of genes that are important for understanding why and how otherwise, by and large, normally developed brains seize.

Key points

- EEG 'abnormalities'/variants in JME, CAE and RE extend beyond their signature EEG traits and are shared with the general population.
- EEG 'abnormalities'/variants in JME, CAE and RE are genetically less complex than the clinical syndromes and are useful endophenotypes.
- Prevalences of EEG 'abnormalities'/variants in JME, CAE and RE (21%, 42% and 33%, respectively) are within the Mendelian inheritance range.
- EEG endophenotypes of JME, CAE and RE should facilitate identification of genes contributing to hypersynchrony in these common epilepsies.

Supplementary data.
Summary didactic slides and supplementary material are available on the www.epilepticdisorders.com website.

References

Akgun Y, Soysal A, Atakli D, *et al*. Cortical excitability in juvenile myoclonic epileptic patients and their asymptomatic siblings: a transcranial magnetic stimulation study. *Seizure* 2009; 18: 387-91.

Alonso ME, Medina MT, Martínez-Juárez IE, *et al*. Familial juvenile myoclonic epilepsy. *Adv Neurol* 2005a; 95: 227-43.

Alonso ME, Medina MT, Martínez-Juárez IE, *et al*. Familial juvenile myoclonic epilepsy. *Adv Neurol* 2005b; 95: 227-43.

Anderman E, Metrakos JD. EEG studies of relatives of probands with focal epilepsy who have been treated surgically. *Epilepsia* 1969; 10: 415.

Atakli D, Soysal A, Atay T, *et al*. Somatosensory evoked potentials and EEG findings in siblings of juvenile myoclonic epilepsy patients. *Epileptic Disord* 1999; 1: 173-7.

Avanzini G, Noebels JL. *Genetics of epilepsy and genetic epilepsies*. Montrouge: John Libbey Eurotext, 2009.

Bali B, Kull LL, Strug LJ, *et al*. Autosomal dominant inheritance of centrotemporal sharp waves in rolandic epilepsy families. *Epilepsia* 2007; 48: 2266-72.

Berg AT, Millichap JJ. The 2010 revised classification of seizures and epilepsy. *Continuum* 2013; 19: 571-97.

Bray PF, Wiser WC. Evidence for a genetic etiology of temporal-central abnormalities in focal epilepsy. *N Engl J Med* 1964; 271: 926-33.

Cavazzuti GB, Capella L, Nalin A. Longitudinal study of epileptiform EEG patterns in normal children. *Epilepsia* 1980; 21: 43-55.

Camfield CS, Striano P, Camfield PR. Epidemiology of juvenile myoclonic epilepsy. *Epilepsy Behav* 2013; 28: S2-7.

Degen R, Degen HE, Roth C. Some genetic aspects of idiopathic and symptomatic absence seizures: waking and sleep EEGS in siblings. *Epilepsia* 1990a; 31: 784-94.

Degen R, Degen HE. Some genetic aspects of rolandic epilepsy: waking and sleep EEG in siblings. *Epilepsy* 1990b; 31: 795-801.

Degen R, Degen HE. Contribution to the genetics of rolandic epilepsy: waking and sleep EEGs in siblings. *Epilepsy* 1992; 6: 49-52.

Delgado-Escueta AV. Advances in genetics of juvenile myoclonic epilepsies. *Epilepsy Curr* 2007; 7: 61-7.

Doose H, Gerken H, Horstmann T, *et al*. Genetic factors in spike-wave absences. *Epilepsia* 1973; 14: 57-75.

Fnais N, Soobiah C, Chen MH, *et al*. Harassment and discrimination in medical training: a systematic review and meta-analysis. *Acad Med* 2014; 89: 817-21.

Gibbs FA, Gibbs EL, Lennox WG. Electroencephalographic classification of epileptic patients and control subjects. *Arch Neurol Psychiatry* 1943; 50: 111-28.

Heijbel J, Blom S, Rasmuson M. Benign epilepsy of childhood with centrotemporal EEG foci: a genetic study. *Epilepsia* 1975; 16: 285-93.

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539-58.

Jayalakshmi SS, Mohandas S, Sailaja S, *et al*. Clinical and electroencephalographic study of first-degree relatives and probands with juvenile myoclonic epilepsy. *Seizure* 2006; 15: 177-83.

McGowan J, Sampson M, Lefebvre C. An evidence based checklist for the peer review of electronic search strategies (PRESS EBC). *Evid Based Libr Inf Pract* 2010; 5: 149-54.

Metrakos K, Metrakos JD. Genetics of convulsive disorders. II. Genetic and electroencephalographic studies in centrencephalic epilepsy. *Neurology* 1961a; 11: 474-83.

Metrakos K, Metrakos JD. Is the centrencephalic EEG inherited as a dominant? *Electroencephalogr Clin Neurophysiol* 1961b; 13: 289.

Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1.

Pal DK, Ferrie C, Addis L, *et al*. Idiopathic focal epilepsies: "the lost tribe". *Epileptic Disord* 2016; 18: 1-37.

Panayiotopoulos CP. *A clinical guide to epileptic syndromes and their treatment*. New York: Springer Publishing, 2010.

Panayiotopoulos CP, Bureau M, Caraballo RH, *et al*. Idiopathic focal epilepsies in childhood. In: *Epileptic syndromes in infancy, childhood and adolescence*. 5th Ed. Bureau M, Genton P, Dravet C, *et al*. Montrouge, France: John Libbey Eurotext, 2012.

Penfield W. Epileptic automatism and centrencephalic integrating system. *Res Publ Assoc Res Nerv Ment Dis* 1952; 30: 513-28.

Serra D, Congiu R, Minafra L, *et al*. EEG trait analysis in siblings of patients with benign rolandic epilepsy. *Bollettino-Lega Italiana Contro L'Epilessia* 2001; 113-4: 267-8.

Tsuboi T, Christian W. On the genetics of the primary generalized epilepsy with sporadic myoclonias of impulsive petit mal type. *Humangenetik* 1973; 19: 155-82.

Valdamudi L, Kjeldsen MJ, Corey LA, *et al*. Analyzing the etiology of benign rolandic epilepsy: a multicenter twin collaboration. *Epilepsia* 2006; 47: 550-5.

Verrotti A, Matricardi S, Di Giacomo DL, *et al*. Neuropsychological impairment in children with rolandic epilepsy and in their siblings. *Epilepsy Behav* 2013; 28: 108-12.

Verrotti A, Casciato S, Spalice A, *et al*. Coexistence of childhood absence epilepsy and benign epilepsy with centrotemporal spikes: a case series. *Eur J Paediatr Neurol* 2017; 21: 570-5.

Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; 36: 1-48.

Wandschneider B, Kopp UA, Kliegel M, *et al*. Prospective memory in patients with juvenile myoclonic epilepsy and their healthy siblings. *Neurology* 2010; 75: 2161-7.

Wells GA, Shea B, O'Connell D, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2014.

TEST YOURSELF

(1) What is the approximate reported prevalence of EEG abnormalities in first-degree relatives of patients with juvenile myoclonic, childhood absence and Rolandic epilepsies?
A. 0-1%
B. 10-20%
C. 20-50%

(2) Are the reported EEG abnormalities in first-degree relatives of patients with juvenile myoclonic, childhood absence and Rolandic epilepsies true abnormalities?

(3) Are EEG changes found in relatives of patients with juvenile myoclonic, childhood absence and Rolandic epilepsies developmental stage specific?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".

Appendix 1. Quality of included studies.

First author	Year	Representativeness of the exposed cohort	Ascertainment of exposure	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Adequacy of response rate
Alonso	2005	B	A	C	A	A
Atakli	1999	B	A	A	D	A
Akgun	2009	B	A	A	D	A
Jayalakshmi	2006	B	D	C	A	A
Tsuboi	1973	A	C	A	B	A
Wandschneider	2010	C	D	A	D	A
Metrakos	1961	A	A	B	A	
Degen	1990	B	D	C	D	A
Doose	1973	C	D	B	A	A
Bali	2007	B	A	A	A	A
Degen	1990	B	D	C	D	A
Verrotti	2013	B	D	A	A	B
Serra	2001	D	D	C	D	D
Heijbel	1975	A	A	C	B	A

Newcastle Ottawa Scale

Selection
1) Representativeness of the exposed cohort
   a) Truly representative of the average individual
   b) Somewhat representative of the average individual
   c) Selected group of users
   d) No description of the derivation of the cohort

2) Ascertainment of exposure
   a) Secure record (*e.g.* surgical records)
   b) Structured interview
   c) Written self report
   d) No description

Comparability
1) Comparability of cohorts on the basis of the design or analysis
   a) Study controls for age or gender
   b) Study controls for any additional factor (*e.g.* body mass index, comorbidity)
   c) No control

Outcome
1) Assessment of outcome
   a) Independent blind assessment
   b) Record linkage
   c) Self report
   d) No description

2) Adequacy of response rate
   a) All subjects accounted for
   b) Subjects lost unlikely to introduce bias - small number lost (<10%)
   c) Subject loss >10%
   d) No statement