



Original article

Complex inheritance and parent-of-origin effect in juvenile myoclonic epilepsy

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Abstract

Background: Juvenile myoclonic epilepsy (JME) is an idiopathic generalized epilepsy (IGE) with complex inheritance. Previous studies have suggested maternal inheritance and female excess in IGEs but have not been specific for JME. We investigated evidence for maternal inheritance, female excess and patterns of familial seizure risk in a well-characterized sample of JME families. **Methods:** We ascertained 89 families through a JME proband and 50 families through a non-JME IGE proband. JME families were divided into those with and without evidence of linkage to the *EJM1* susceptibility locus on chromosome 6. We analyzed transmission in 43 multigenerational families, calculated the adjusted sex ratio for JME, and looked for evidence of seizure specific risk in 806 family members. **Results:** We found evidence for preferential maternal transmission in both *EJM1*-linked and unlinked families (2.7:1), evidence even more marked when potential selection factors were excluded. The adjusted female: male risk ratio was very high in JME (RR = 12.5; 95% CI: 1.9–83.7). Absence seizures in JME probands increased the overall risk of seizures in first degree relatives (15.8% vs. 7.0%, $P=0.011$), as well as first-degree relatives' specific risk of absence seizures (6% vs. 1.6%, $P=0.01$), but not myoclonic seizures. **Conclusions:** We have confirmed the finding of maternal inheritance in JME, which is not restricted to JME families linked to the *EJM1* locus. The striking female excess in JME may relate to anatomical and/or endocrine sexual dimorphism in the brain. Evidence for independent inheritance of absence and myoclonic seizures in JME families reinforces a model in which combinations of loci confer susceptibility to the component seizure types of IGE.

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1. Introduction

The idiopathic generalized epilepsies (IGEs) constitute a heterogeneous, clinically classified group of seizure disorders that are likely genetic in origin. Juvenile myoclonic epilepsy (JME) is the one of the most intensively studied forms of epilepsy [1]. Identification of genes and genetic loci for JME [2–7] has been guided and greatly facilitated by concentrating on phenotypic details. For example, by analyzing JME and non-JME forms of IGE

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separately, we showed different patterns of linkage to a susceptibility locus on chromosome 8 [8]; we also found that JME, with its characteristic awakening myoclonic jerks, and awakening forms of ‘grand-mal’ or primary generalized tonic-clonic seizures in IGE, both show evidence of linkage to the *EJMI* locus on chromosome 6 [9]. We found heterogeneity in JME, with some families linked to *EJMI*, and others not linked to *EJMI*; the susceptibility gene at the *EJMI* locus has now been preliminarily identified as *BRD2*, a putative transcriptional regulator [10]. These results suggest that genetic susceptibility loci influence component features of epilepsy such as arousal-related cortical excitability, or photosensitivity, and so on, rather than influencing all idiopathic epilepsies as a whole, or even particular epilepsy syndromes. Thus, by concentrating on phenotypic features, we may get closer to finding susceptibility genes and be able to piece together mechanisms for IGEs from understanding the joint actions of these genes. Investigating three interesting phenotypic features of JME could complete the genetic puzzle: maternal inheritance; female excess; and the occurrence of different seizure types in JME family members.

Although maternal inheritance has often been noted in IGEs as a whole [11–17], it is not clear whether this parent of origin effect applies to all IGEs. True maternal inheritance may reflect a number of mechanisms including mitochondrial inheritance, X-linkage or genomic imprinting (Table 3). We have evidence, from linkage analysis, for maternal inheritance in JME families linked to the *EJMI* locus: the pattern of lodscores is unusual in that they vary only with respect to the female recombination fraction, not the male recombination fraction [18]. There is no known difference between male and female recombination in this part of the human genome, therefore indicating that disease-marker transmission at *EJMI* relates to the maternal and not the paternal allele [18]. Co-segregation of a disease gene with a marker on the maternal allele cannot be explained by either mitochondrial inheritance or X-linkage. Genomic imprinting may explain parent-of-origin effects but could not by itself influence the sex ratio of a disease, as seen in JME.

A female excess in JME has been reported previously. The observation of female disease excess is open to ascertainment bias, because of the well-known phenomenon that females use health services more than males. This is a possible shortcoming of previous epilepsy studies [19–21], but one that can be overcome at the study design stage, as we did below. Sex differences in epilepsy have been related to divergent anatomical patterns of development [22], and to the influence of sex-steroids on neurons [23]. Finding a true sex difference in JME could help to narrow down candidate genes that are involved in one of these processes.

As well as maternal inheritance and female excess, we were intrigued by two observations relating to the distribution of seizures in JME patients and their family members: first, that individuals with JME may or may not

have co-occurring generalized tonic-clonic seizures or absence seizures; and second, that family members of JME patients may be affected with different combinations of myoclonic, absence or generalized tonic-clonic seizure types, but not necessarily always with JME or with myoclonic seizures. This raises the question of whether these different seizure types are inherited separately. We already had evidence from linkage analysis that a major susceptibility locus on chromosome 18 confers risk for most adolescent-onset IGEs; contributing loci at *EJMI* on chromosome 6 influences the expression of myoclonic seizures; and loci on chromosomes 8 and 5 influence the expression of non-myoclonic seizure types [24]. Linkage analysis suggested that different combinations of loci increase susceptibility to absence, myoclonic and GTC seizures. Such a model might explain the occurrence of different combinations of seizure types in JME patients and in their family members.

With these three issues in mind, we used a large collection of well characterized IGE families to ask the following questions. (1) Is there epidemiological support for maternal inheritance in JME? If so, is it limited only to *EJMI*-linked forms of JME? (2) Is there epidemiological evidence of female excess in JME when ascertainment bias is accounted for? (3) Do the risks for different seizure types in JME family members differ according to the seizure types in the JME proband, thus suggesting seizure-specific transmission of risk?

2. Methods

2.1. Data collection

Patients with typical forms of adolescent-onset IGE were identified through neurologists in the northeastern USA (see authors) from 1990 onwards. Probands had diagnoses of JME, juvenile absence epilepsy (JAE), or epilepsy with generalized tonic-clonic seizures (EGTCS). Diagnoses were confirmed from patient charts, investigations, and personal interview, in accordance with the classification of epilepsy and epilepsy syndromes established by the International League Against Epilepsy [25]. Families were ascertained through a single patient with IGE, with only the presence of at least one other sibling required, either affected or unaffected. Once the proband diagnosis was confirmed, we ascertained the rest of the family, starting with the siblings, parents and offspring, if any. We only collected data from second degree or more remote relatives if one of them had a confirmed diagnosis of epilepsy. We recorded 1 h EEGs on all consenting family members of the proband over the age of 8 years, looking for epileptiform activity such as generalized spike and wave discharge. EEG recordings were analyzed and reported by a trained neurophysiologist (MD and LR). Clinical history was recorded from all family members independently at

interview, blood was drawn for DNA extraction and subsequent genetic analyses. The study was approved by the institutional review board of all relevant institutions. All participating patients and family members gave their informed consent.

2.2. Patients and families

Data on 139 IGE probands were collected for this study: 89 probands had a diagnosis of JME; 13 had JAE; 37 had EGTCS with either awakening ‘grand mal’ or random ‘grand mal’ (generalized tonic-clonic) seizures occurring at random times of the day. The age of onset for JME was between 11 and 18 years in 80% of cases; the mean age of onset for myoclonic jerks was 14.6 years, and for GTC seizures in JME, 15.9 years. Median age of onset was slightly younger in females (13 years) compared to males (14 years). Most probands with JME had GTCS ($n=77$ or 87%), but only 24 (29%) had absence seizures (all except one were juvenile absence type). However, absence seizures were twice as frequent in female JME probands (31%) compared to male JME probands (17%), whereas there was no sex difference for GTCS in JME probands. JAE probands had onset between 8 and 17 years, 5 of 13 had GTCS; EGTCS probands had a mean age of onset of 15 years. Sex distribution in probands is shown in Table 1.

Clinical data were available on 590 first degree and 216 second degree relatives. Epilepsy and seizure diagnostic definitions in relatives of probands were the same as for probands, with the exception that some relatives had seizures which were focal, symptomatic, or unclassifiable.

2.3. Statistical analysis

We sorted transmission patterns in 43 multigenerational IGE families (26 of them with JME probands) according to the pattern of affected family members. Thus, if the mother of a JME proband had a form of IGE, we assigned maternal inheritance for JME in that family. We examined both the diagnoses of parents of JME probands and the diagnosis of offspring of JME affecteds. This approach is an incomplete approximation because it is limited to clinical symptoms and signs of seizures, which may be absent in some individuals if the penetrance of the trait is low, or if the inheritance is recessive. We stratified families in which

the proband had JME into two groups: (i) families with evidence for, or (ii) families with evidence against linkage to the *EJMI* locus. Evidence for linkage was derived from previous analysis of these families [24]. When examining the question of female excess, we calculated binomial confidence intervals for sex ratios. Adjustment for possible ascertainment bias in the sex ratio was made by examining non-proband cases separately.

We also calculated the risk of seizures in relatives, looking for variation according to the combination of seizure types and sex of the JME proband. We calculated the prevalence of epilepsy syndromes, seizures, and epileptiform EEGs in first- and second-degree relatives, according to the IGE type in the proband. This analysis was designed to identify patterns of seizure aggregation. Comparison of proportions used chi-squared or Fisher’s exact tests. All analyses were performed using Stata SE for Macintosh 8.0 [26].

3. Results

3.1. Maternal inheritance in JME

There was evidence for preferential maternal transmission of JME, both from mothers to JME probands, and from JME affected mothers to their offspring. Mothers of JME probands were significantly more often affected with epilepsy or generalized spike-wave EEG trait than fathers of probands (22 vs. 4, $P=0.0005$). In 19 IGE families containing JME cases who were not probands (and therefore not subject to selection bias), we observed 12 cases apparently matrilineally inherited, one patrilineally, and in six cases the lineality could not be determined from the pedigree structure. We found no incidence of transmission of JME through a JME affected father to his offspring. We looked at the two genetic forms of JME, those from families with evidence of linkage to the *EJMI* locus on chromosome 6, and those without evidence of linkage to *EJMI*: evidence for maternal inheritance predominated in both types of family. These findings suggest that maternal inheritance predominates in JME and is not exclusive to *EJMI*-linked families.

3.2. Female excess in JME

There was significant excess of females amongst JME probands (2.7:1), in contrast to the near equal sex ratio in non-JME IGE probands (1.1:1). To exclude potential sex bias in the selection of probands, we separately examined only ‘secondary’ cases, i.e. individuals with JME who had been detected through searching the family of a proband. In these secondary JME cases the female excess was even more striking (20:1). The 21 secondary JME cases came from 19 unrelated families, therefore could not be explained by clustering of female cases in a handful of families with

Table 1
Diagnoses in IGE probands by sex

Diagnosis of proband	Male (%)	Female (%)
JME	24 (27)	65 (73)
JAE	8 (62)	5 (38)
EGTCS	20 (54)	17 (46)
Total	52 (37)	87 (63)

JME, juvenile myoclonic epilepsy; JAE, juvenile absence epilepsy; EGTCS, epilepsy with generalized tonic-clonic seizures; IGE, idiopathic generalized epilepsy.

unusual sex-linked transmission patterns. In these 19 families the risk ratio for seizures in females compared to males was 12.5 (95% CI: 1.9–83.7). We repeated stratification by *EJMI* linkage evidence, but found no significant difference in the sex ratio in linked and unlinked families. In comparison, there was no significant excess female risk in secondary JAE cases (RR 0.42; 95% CI: 0.05–3.76) or secondary EGTCS cases (RR 1.28; 95% CI: 0.32–5.16). Female excess in JME is marked, not explained by selection bias, and not seen in other forms of adolescent-onset IGE in our sample.

3.3. Seizure risk in relatives of JME probands

The overall risk of epilepsy in first-degree relatives of IGE probands was 8.0% (Table 2). The risk of any seizures in relatives of JME probands differed according to whether the JME proband had absence seizures or not. If the JME proband did not have absence seizures, the overall risk of any seizures in first degree relatives was 7.0%; however, if

the JME proband did have absence seizures, the overall risk of any seizures in first degree relatives rose to 15.8% ($P=0.011$).

Furthermore, absence seizures in the JME proband increased the specific risk of absence seizures in first-degree relatives (6% vs. 1.6% if JME proband had no absence seizures, $P=0.01$). Absence seizures in the JME proband were associated with a borderline increase in risk of GTCS in first-degree relatives (10% vs. 5% if the JME proband had no absence seizures, $P=0.06$). Absence seizures in the JME proband were not associated with increased risk of myoclonic seizures in first degree relatives (5% vs. 4%, $P=0.7$).

In comparison, whether or not GTCS were present in JME probands did not alter the overall (or specific) risk of afebrile seizures in first degree relatives (9% vs. 7%, $P>0.99$).

These analyses suggest that the factor increasing risk for absence seizures in JME families is independent of the factor influencing myoclonic seizures. The risk for absence seizures in these JME families may possibly be shared with an increased risk of GTCS.

Table 2
Epilepsy diagnoses in first- and second-degree relatives

	Epilepsy diagnosis of proband			
	JME	JAE	EGTCS	Total
<i>1° relatives</i>				
Normal	347	48	138	533
Affected epilepsy (%)	35 (9)	4 (7.7)	8 (5.4)	47 (8.0)
JME	14	1	3	18
JAE/CAE	9	1	2	12
EGTCS	7	2	3	12
Focal/Unclassified ^a	5	0	0	5
Symptomatic				
EEG GSW only	4	2	3	9 (2.3%)
Missing epilepsy data	7	0	3	10
Total	389	52	149	590
<i>2° relatives</i>				
Normal ^b	140	25	40	205
Affected epilepsy (%)	8 (5.4)	1 (3.8)	2 (4.8)	11 (5.1)
JME	2	0	0	2
JAE/CAE	2	0	0	2
EGTCS	3	0	2	5
Focal/Unclassified/	1	1	0	2
Symptomatic				
EEG GSW only	1	0	0	1 (1.9)
Missing epilepsy data	0	0	0	0
Total	148	26	42	216

The prevalence of epilepsy and seizures in relatives of IGE probands was up to eight times higher than in unrelated family members (1%): highest for relatives of JME probands, intermediate for relatives of JAE probands and lowest for relatives of EGTCS probands; amongst relatives, highest in siblings (10.5%), intermediate in offspring (7.0%), and lowest in parents (5.4%). GTCS was the most common seizure type (75% in affected first degree), as it was in probands (85%); febrile seizures were reported in 2.6% of first degree relatives; focal or symptomatic seizures were present in 1% of first or second degree relatives. JME, juvenile myoclonic epilepsy; JAE, juvenile absence epilepsy; CAE, childhood absence epilepsy; EGTCS, epilepsy with generalized tonic-clonic seizures; generalized spike-wave (GSW) on EEG only.

^a Symptomatic seizures secondary to alcohol or illicit drug use, labour, and senile dementia.

^b Note that information was only systematically collected from second degree relatives if one of them had a confirmed diagnosis of epilepsy.

4. Discussion

We had three major findings. First, we found strong epidemiological support for maternal inheritance in JME families, both linked and unlinked to *EJMI*. Second, we observed pronounced female excess amongst JME affecteds, even more pronounced when we accounted for possible selection bias. Third, familial seizure risks suggested independent inheritance of absence and myoclonic seizures within JME families. How do these observations contribute to the elucidation of genetic mechanisms in JME?

4.1. Parent-of-origin effect in JME

Our previous linkage analysis of JME suggested maternal inheritance in families linked to the *EJMI* locus [18]. The present study, using an expanded dataset and different analytic approach, confirms maternal inheritance in JME, in both families that show linkage to *EJMI* and families with evidence against linkage to *EJMI*. Maternal inheritance has been noted in the past, in epilepsy family and epidemiological studies in general [11–17], as well as in family studies restricted to JME. In JME family studies, offspring of JME affected mothers show a five times higher risk of epilepsy than offspring of JME affected fathers [16,27]; and JME is more often transmitted through IGE affected mothers than through IGE affected fathers [19]. Absence seizures, e.g. in CAE, are more common in females. Higher seizure risk in offspring of mothers may be confounded by higher incidence of absence seizures in females [27], but as our results and other studies show,

absence seizures do not explain the increased maternal risk for seizure transmission [17,28,29]. We can conclude that there is reasonably consistent evidence in favor of maternal inheritance in JME in a variety of study designs. But what is the underlying biology explaining this observed phenomenon?

Many explanations have been proposed and excluded for maternal inheritance in epilepsy [17,30] (Table 3). To date there has been no evidence of linkage of JME to markers on the X chromosome, nor evidence of mitochondrial mutations. Neither is there sufficient evidence for perinatal or intra-uterine factors influencing the expression of JME. Genomic imprinting remains an untested hypothesis that is attractive because of recent discoveries about imprinting control of the development of different brain regions: in mice, the development of the telencephalon is dependent almost exclusively on maternally expressed alleles, while the development of the diencephalon depends on expression of paternally expressed alleles [31]. Two human disorders of early neurodevelopment which originate from disturbances in diencephalic and telencephalic structures, Prader–Willi syndrome and Angelman syndrome respectively, have their genetic basis in imprinting faults [32]. A molecular search for imprinting centers or differential allelic expression in JME susceptibility genes such as *BRD2* is a reasonable and simple next step to test the hypothesis of imprinting.

4.2. Female excess

There are few if any biological mechanisms that can satisfactorily explain both maternal inheritance and female excess, and the likely conclusion is that there are two separate mechanisms operating. The high female to male JME sex ratio in our data, adjusted for overall sex ratio in the sample, confirms nearly all previous findings of female excess [19–21], and makes selection bias a less likely alternative explanation. Two theoretical types of selection bias deserve consideration, as well as random sampling

variation: first, females *with* affected female relatives might be more willing to participate in this study; however, we found an equal sex ratio among potential research subjects who were unwilling to participate (data not shown); second, males may recall myoclonic seizures less well than females, but the stringency of our interviews (each family member is individually questioned for symptoms), makes this explanation unlikely. In any case, one would have to propose a very high rate of concealment among males to explain this degree of female excess.

There is a myriad of possible genetic and non-genetic mechanisms that might explain female excess in epilepsy. The simplest explanation would be that expression of genes underlying seizure susceptibility is upregulated by sex-steroids beginning at puberty [33]. There is abundant evidence that neuroactive steroids, both endogenous to the brain and from outside the brain, can regulate the transcription of genes as well as modulate protein synthesis or degradation [23]; neuroactive steroids can also influence synaptogenesis [34], and modulate neural excitability [35]. A less direct explanation is that susceptibility to generalized seizures is mediated in part by brain structures which show sexual dimorphism: for example, regions of the thalamus and other nuclei differ in size between the sexes [36], as does the relative volume of gray to white matter [37]. Sex specific differences affecting brain regions involved in the generation of specific seizure types may be a better explanation for why we find female excess in only certain types of epilepsy, rather than in all epilepsies [38]. Nonetheless, there is currently no persuasive evidence favoring any particular biological mechanism of female excess in JME.

4.3. Complex inheritance

Our findings point to independent inheritance of absence and myoclonic seizures in JME families. This further suggests that IGE syndromes arise from the joint action of

Table 3
Patterns of parental transmission and offspring sex ratio expected from various genetic and non-genetic models

	Expected patterns	
	Parental transmission	Sex ratio in offspring
X-linked recessive	Maternal, mothers not affected	Only boys affected
X-linked dominant	Either maternal or paternal	Equal if maternal transmission Female only if paternal transmission
Mitochondrial	Maternal	Equal, with variable expression
Triplet repeat	Either maternal or paternal	Equal, with anticipation
Ascertainment bias	Either maternal or paternal	Female or male excess
Non-paternity	Maternal	Equal
Perinatal or pregnancy factors	Maternal	Variable, depending on factors
Paternal imprinting	Maternal	Equal
Sex-dependent penetrance	Either maternal or paternal	Female or male excess

Most alternative explanations for maternal inheritance in epilepsy such as ascertainment bias, nonpaternity, prenatal or perinatal factors have been excluded. There is no evidence for mitochondrial inheritance, which is associated with *progressive* myoclonic epilepsy and affects other organs as well as the brain, in contrast to the symptoms in JME. Neither has there been any evidence for X linkage in published genome scans of JME [24,41]. Trinucleotide-repeat expansions have not been found, nor is there evidence of anticipation in multigenerational JME families.

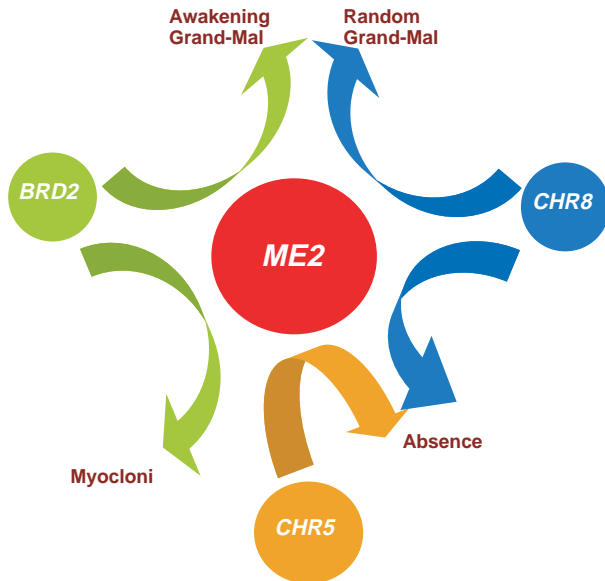


Fig. 1. Proposed model of oligogenic interaction in adolescent-onset IGEs, derived from whole genome linkage analysis [24]. Circles denote susceptibility loci on different chromosomes. For example, a combination of the *BRD2* gene and *ME2* gene [40] increases susceptibility to myoclonic seizures; combination of loci on chromosomes 5 and *ME2* gene [40] increases susceptibility to absence seizures. This model is consistent with results from the present study which suggest that risks for absence and myoclonic seizures are independent within JME families.

genes influencing different seizure types in individuals. Another research group has reached similar conclusions using separate epidemiological data [39]. The evidence is building that susceptibility genes influence symptoms of epilepsy, such as seizure types, rather than influencing epilepsy syndromes themselves. Findings from our linkage analysis of IGE families also lend support to the idea of genotypes influencing seizure types (Fig. 1). Linkage analysis yielded evidence for a major susceptibility locus on chromosome 18 conferring risk for most adolescent-onset IGE types (now identified as the *ME2* gene [40]); a modifying locus on chromosome 6 (now identified as the *BRD2* gene) influencing expression of myoclonic seizures; and loci on chromosomes 8 and 5 influencing the expression of non-myoclonic and absence seizure types, respectively [24]. We proposed a model in which combinations of major and modifying loci conferred susceptibility to different primary generalized seizure types in adolescent-onset IGE.

Concentrating on phenotype to guide genetic analysis in epilepsy has produced dividends as well as complications. Subtyping on clinical features has given us a framework to understand issues of heterogeneity in the epilepsies and increased our ability to detect susceptibility genes in linkage analysis. At the same time, we find that the tools of genetic epidemiology are not sharp enough to dissect problems as complicated as maternal inheritance and female excess. In order to solve these intriguing problems we need to turn to molecular methods that can directly test hypotheses of

imprinting and sex-dependent penetrance as explanations for maternal inheritance and female excess.

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