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FULL-LENGTH ORIGINAL RESEARCH

Quantitative trait locus on distal chromosome 1 regulates the occurrence of spontaneous spike-wave discharges in DBA/2 mice

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Summary

Purpose: Most common forms of human epilepsy result from a complex combination of polygenetic and environmental factors. Quantitative trait locus (QTL) mapping is a first step toward the nonbiased discovery of epilepsy-related candidate genes. QTL studies of susceptibility to induced seizures in mouse strains have consistently converged on a distal region of chromosome 1 as a major phenotypic determinant; however, its influence on spontaneous epilepsy remains unclear. In the present study we characterized the influence of allelic variations within this QTL, termed *Szs1*, on the occurrence of spontaneous spike-wave discharges (SWDs) characteristic of absence seizures in DBA/2 (D2) mice.

Methods: We analyzed SWD occurrence and patterns in freely behaving D2, C57BL/6 (B6) and the congenic strains D2.B6-*Szs1* and B6.D2-*Szs1*.

Key Findings: We showed that congenic manipulation of the *Szs1* locus drastically reduced the number and the duration of SWDs in D2.B6-*Szs1* mice, which are homozygous for *Szs1* from B6 strain on a D2 strain background. However, it failed to induce the full expression of SWDs in the reverse congenic animals B6.D2-*Szs1*.

Significance: Our results demonstrate that the occurrence of SWDs in D2 animals is under polygenic control and, therefore, the D2 and B6 strains might be a useful model to dissect the genetic determinants of polygenic SWDs characteristic of typical absence seizures. Furthermore, we point to the existence of epistatic interactions between at least one modifier gene within *Szs1* and genes within unlinked QTLs in regulating the occurrence of spontaneous nonconvulsive forms of epilepsies.

KEY WORDS: Epilepsy, Spike-wave discharges, EEG, Quantitative trait loci, Congenic mice.

The etiology of the epilepsies is hypothesized to be influenced strongly by genetic factors. Mutations have been discovered for several rare Mendelian forms of epilepsy; however, because more common forms of epilepsy such as idiopathic generalized epilepsy (IGE) rely on polygenic and environmental interactions, advances are needed for understanding their biologic basis and the underlying mechanisms (Steinlein, 2004).

One approach that allows the nonbiased discovery of epilepsy-related candidate genes is the use of quantitative trait locus (QTL) mapping in common inbred strains of laboratory mice that model complex heritable seizure traits (Frankel, 2009).

Previous studies have documented that the distal region of chromosome 1 contains a QTL termed *Szs1* that is in large part responsible for the known difference in seizure susceptibility between C57BL/6 (B6) and DBA/2 (D2) mice (Ferraro et al., 1997, 1999, 2001). However, the QTL studies that isolated *Szs1* used induced convulsive seizures as a phenotypic marker and, therefore, its influence on spontaneous epilepsy remains to be clarified.

A striking feature of the D2 strain, not present in B6, is the frequent occurrence of high-amplitude, 6–8 Hz spike and waves discharges (SWDs), which represent an endophenotype of thalamocortically generated SWDs typical of absence seizures, one of the most common forms of IGE (Ryan & Sharpless, 1979; Crunelli & Leresche, 2002). Indeed as in all models of absence seizure, SWDs in D2 mice are associated with behavioral arrest (Ryan, 1984). They are strongly reduced by antiabsence medication

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(Marrosu et al., 2007), and their occurrence is increased and suppressed by the administration of γ-aminobutyric acid $(GABA)_B$ agonists and antagonists, respectively (Marrosu et al., 2006).

In the present study, using reciprocal congenic strains B6.D2-*Szs1* and D2.B6-*Szs1* that were generated previously (Ferraro et al., 2004), we have carried out a comprehensive evaluation of the impact of allelic variation(s) within the QTL *Szs1* on the inherited occurrence of the generalized nonconvulsive spontaneous SWDs of D2.

Methods

Animals

Inbred mouse strains C57BL/6 (B6) and DBA/2 (D2) were bred in-house at the Research Service of the Veterans Affairs Medical Center in Coatesville, PA, U.S.A., using mating pairs purchased from The Jackson Laboratory (Bar Harbor, ME, U.S.A.). Congenic strains were obtained as described by Ferraro et al. (2004). D2.B6-*Szs1* mice have a genetic background that is derived essentially from the D2 strain, but they are homozygous for a fragment of distal chromosome 1 (about 40 cM between markers D1Mit390 and D1Mit 17) from the B6 strain. On the other hand, B6.D2-*Szs1* mice are homozygous between markers D1Mit30 and D1Mit17 from the D2 strain on a B6 strain background.

Surgical procedures

Adult male mice, 10–14 weeks of age (26–30 g), were anesthetized with ketamine (80 mg/kg) and xylazine (16 mg/kg) as one intraperitoneal injection. Two burr holes were drilled to house electroencephalography (EEG) electrodes over the frontal areas of both hemispheres (−2.0 mm bregma, 1.0 mm lateral). Teflon-coated silver wire was used to make ball electrodes (1 mm in diameter) for EEG recording. A stainless steel screw was used as the ground electrode. The electromyography (EMG) electrodes were sutured to dorsal nuchal muscle, and the EMG was recorded in a bipolar configuration.

Recording procedures

Animals were allowed 10 days to recover from surgery. Experiments were carried out in a sound-attenuated sleep-recording chamber with a 12 h lights-on and 12 h lights-off. EEG signals were calibrated, amplified, and filtered between 0.1 and 500 Hz, and they were digitized at a sample rate of 1 kHz. EMG signals were filtered between 1 and 100 Hz. The signals were recorded for each mouse for >4 h per day over multiple days.

Data analysis

EEG traces were analyzed by performing power spectrum with a fast Fourier algorithm using custom software written in Igor (Wavemetrics, Oswego, OR, U.S.A.). Quantification of SWDs was done with a custom algorithm that detects the presence of at least two high-amplitude spikes at 1–15 Hz, 2.5 times the amplitude of the root-mean-square of the background activity. Characteristics of SWDs (duration, frequency, and occurrence) were compared between strains using Mann-Whitney *U*-test.

Results

In order to characterize the influence of the locus *Szs1* on the nonconvulsive SWDs of D2 mice, we recorded the baseline EEG from nonanesthetized, chronically implanted B6 and D2, and their reciprocal congenic strains. In all four groups, EEG showed spontaneous transitions from waking to sleep. We classified states of vigilance according to standard criteria (Erwin et al., 1984) as illustrated in the example B6 mouse in Fig. 1. During alert waking (AW), animals were behaviorally active and showed a high-amplitude EMG (Fig. 1, upper panel and detail a). EEG was rich in low-amplitude theta, with a spectral peak centered at 8 Hz (range 6–9 Hz), as well as in fast frequencies above 15 Hz, which included the beta and gamma bands (Fig. 1 detail a, right column, power spectrum). During quiet waking (QW) the EMG did not show overt signs of movement and the EEG remained of low amplitude and rich in theta and fast frequencies (Fig. 1, detail b). The transition to slow wave sleep (SWS) was characterized by an increase in the amplitude of the EEG, an increase in power in the delta (0.5–4 Hz) frequency band, a clear peak at the frequency of sleep spindles (∼10 Hz), and the diminution of fast frequencies >15 Hz and theta band activity (Fig. 1, detail c). Deepening of sleep was characterized by a further increase in EEG amplitude dominated by activity in the delta frequency range (Fig. 1, detail d). Finally, rapid eye movement (REM) sleep was characterized by a dominant theta (6–8 Hz) frequency activity, visible by simple inspection of the EEG and by a large spectral peak centered at 8 Hz (Fig. 1, detail e).

The EEG recordings of D2 mice also showed the electrographic signs that characterize wake-sleep cycles (Fig. 2). However, the spontaneous EEG of D2 mice was distinguished by the presence of bilaterally expressed SWDs (Fig. 2A, detail a) and large amplitude single spikes (Fig. 2A, detail b; n = 11 of 11 mice). SWDs consisted of large amplitude rhythmic waves at 6–9 Hz (7.4 ± 0.5 Hz, mean ± standard deviation [SD]) that can last several seconds (mean = 1.48 ± 0.31 s, range 1–5 s). Single spikes were large-amplitude isolated events lasting 50–100 msec and recurring irregularly. SWDs were easily distinguishable from sleep spindles by (1) their abrupt onset (in contrast with the waxing nature of spindles), (2) their higher amplitude (spindles are 300–400 μV), and (3) their prevalence during QW (spindles are the hallmark of slow wave sleep). Neither SWDs nor single spikes were ever observed in B6 mice (n = 0 of nine mice).

The overall rate of occurrence of SWDs in D2 mice was 7.7 ± 2.6 per hour. They appeared mostly during QW

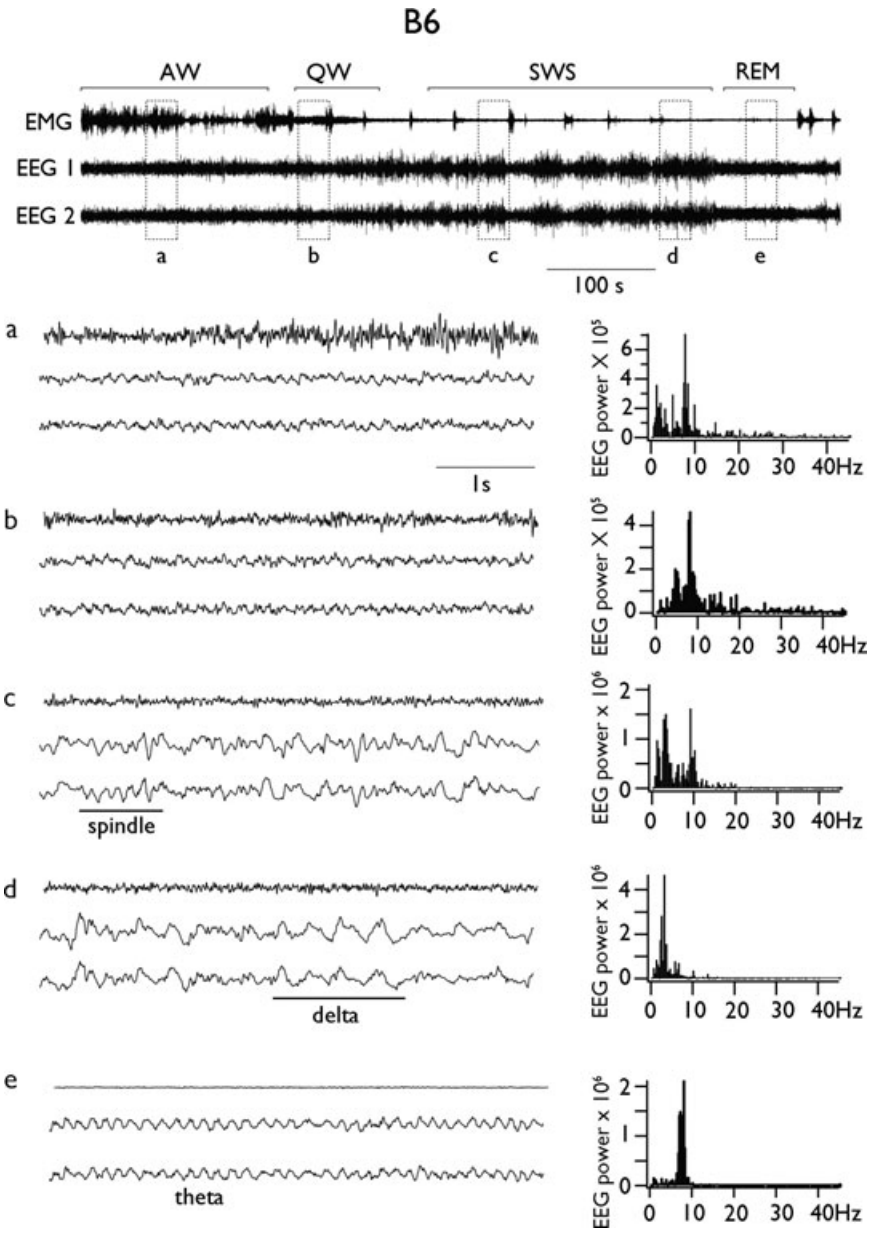

Figure 1.
Spontaneous transition from wake to sleep in freely behaving B6 mice. Upper panel shows a representative continuous bilateral EEG recording from a B6 mouse alongside EMG recording. Detail **a**: alert waking (AW). Detail **b**: quiet waking (QW). Detail **c**: epoch of slow wave sleep (SWS) with a boot of spindles oscillations. Detail **d**: epoch of SWS with a boot of activity in the delta frequency range. Detail **e**: Rapid eye movement (REM) sleep. On the right are displayed the power spectra derived from the EEG traces situated on the left.

(46.1 ± 10.5 per hour; indicated by asterisks in Fig. 2A), and were less frequent during slow wave sleep (SWS; 4.3 ± 1.7; $p < 10^{-6}$), during which they seemed to develop during sleep spindles as an abnormal increase in amplitude and decrease in frequency of the ongoing spindling oscillation (Fig. 2B). When SWDs appeared during AW, they were associated with an arrest of movement (Fig. 2C), similar to SWD characteristic of absence seizures in most species including humans (Blumenfeld, 2005). The representative examples of SWDs depicted in Fig. 3 show a clear peak in the frequency spectrum at 7 Hz.

In the congenic D2.B6-*Szs1* mice (Fig. 3A), in which most of the genome is from the D2 strain except for the small portion of chromosome 1 containing *Szs1* from B6, spontaneous SWDs (Fig. 3A asterisks, detail a) and single spikes (Fig. 3A, detail b) occurred in all mice (n = 10 out of 10). However, compared to SWDs in the D2 strain, these occurred at much lower overall rates (2.8 ± 1.1 per hour; $p < 10^{-5}$; Fig. 3C). When analyzing only the periods of QW, their rate of occurrence was significantly lower as well (11.1 ± 3.8 per hour; $p < 10^{-5}$; Fig. 3D) and their duration was dramatically reduced (411 ± 101 msec; $p < 10^{-5}$; Fig. 3F). In addition, the intra-SWD frequency was slightly higher (8.2 Hz ± 0.8; $p < 0.01$; Fig. 3E). These differences were not due to variations of time spent in different behavioral states. Indeed, for comparisons, the EEG from each animal was analyzed for 2 h of QW, 6 h of AW, 13 h of SWS, and 1 h of REM. Furthermore, all the data were

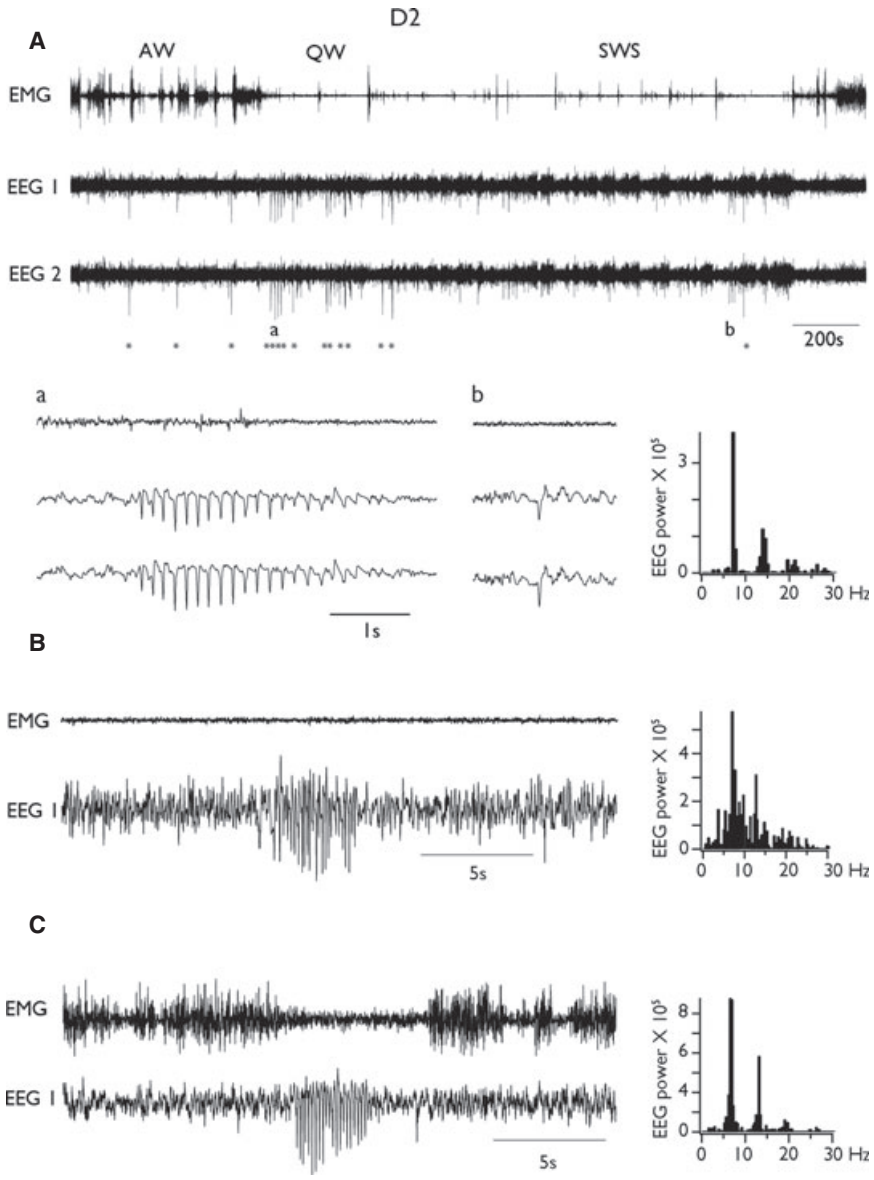

Figure 2.
Spike wave discharge (SWDs) occurrence in freely behaving D2 mice. (**A**) Upper panel shows a representative continuous bilateral EEG recording from a D2 mouse alongside an EMG recording. The stars indicate the occurrence of SWDs. Note the increase in the occurrence of SWDs during quiet wakefulness (QW) compared to active waking (AW) and slow wave sleep (SWS). Detail **a**: typical example of SWDs during QW. Detail **b**: typical example of isolated large-amplitude single spike during SWS. (**B**) Example of SWDs occurring during SWS. (**C**) Example of SWDs occurring during AW. Note the decrease in EMG amplitude during SWDs. On the right are displayed the power spectra computed during the seizure episodes on the EEG traces situated on the left.

extracted from recordings made at similar daily hours (between 2 and 6 p.m.).

In the congenic B6.D2-*Szs1* mice, in which the same small portion of chromosome 1 is now from D2, spontaneous single spikes and SWDs (Fig. 3B) were present in three of nine animals. In the animals that presented SWDs, the events were seen only occasionally (0.6 ± 0.2 per hour) and thus were significantly less frequent than in D2 and D2.B6-*Szs1* mice ($p < 0.003$ and $p < 0.003$, respectively; Fig. 3C). When they occurred, SWDs in B6.D2-*Szs1* mice were of shorter duration (0.72 ± 0.10 s; Fig. 3F) than in D2 but lasted longer than in D2.B6-*Szs1* mice ($p < 0.003$ and $p < 0.003$, respectively; Fig. 3F). Of interest, the frequency of the SWDs in B6.D2-*Szs1* mice was between 2 and 4 Hz (3.1 ± 0.3 Hz; Fig. 3E), which is similar to human SWDs (Crunelli & Leresche, 2002).

Discussion

We show that congenic manipulation of the *Szs1* locus drastically reduced the number and the duration of SWDs in D2.B6-*Szs1* mice; however, it failed to induce the full expression of SWDs in B6.D2-*Szs1*. Our results demonstrate that the occurrence of SWDs in D2 animals is under a polygenic control and, therefore, D2 and B6 strains might be a useful model to dissect the genetic determinants of polygenic SWDs characteristic of typical absence seizures (Crunelli & Leresche, 2002).

Indeed, although single gene manipulation can lead to SWDs in mice (reviewed in Noebels, 2003), several recent studies demonstrated the importance of the genetic background (Strohl et al., 2007; Beyer et al., 2008; Papale et al., 2009). The present results point to the existence of epistatic

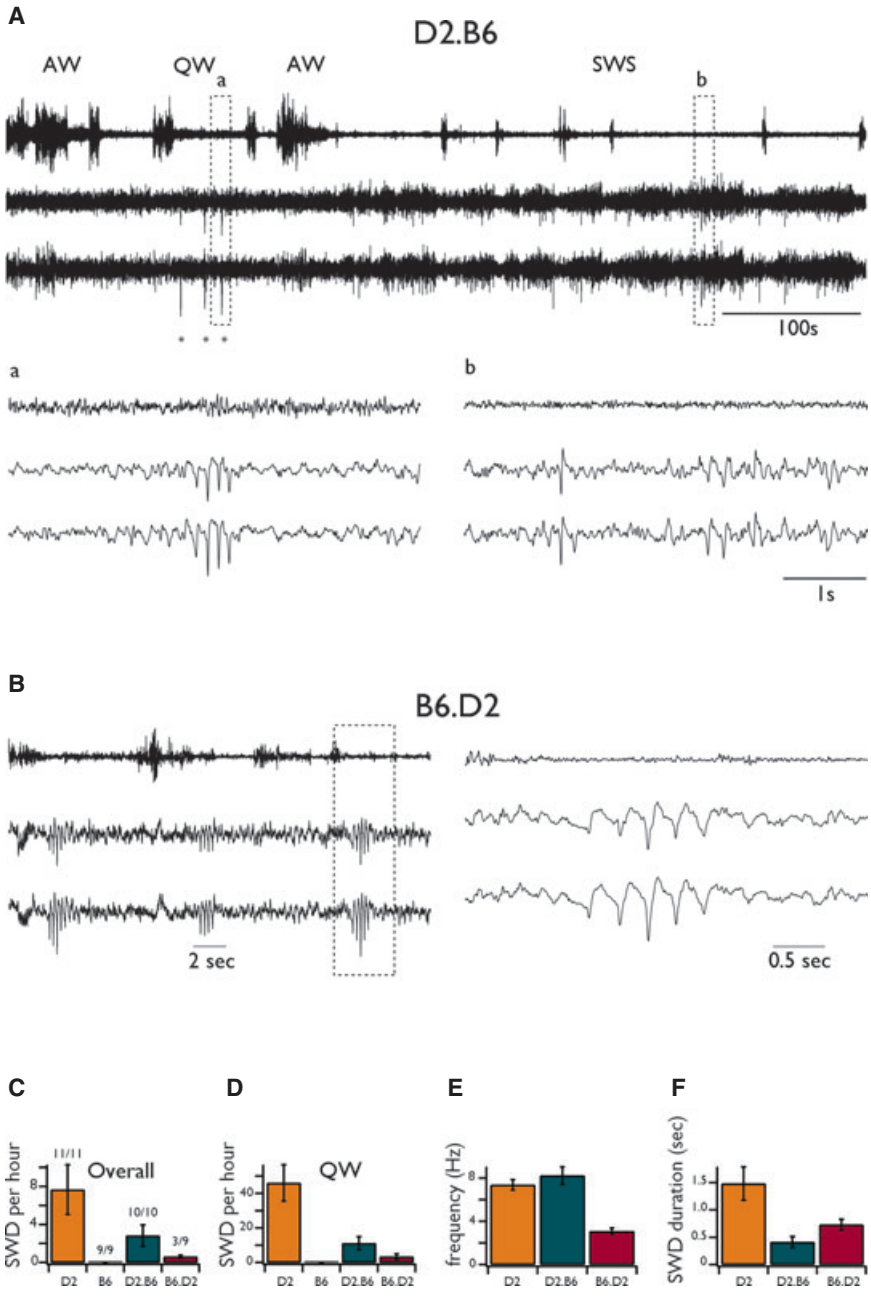

Figure 3.
Spike wave discharge (SWD) occurrence in freely behaving reciprocal congenic mice. (**A**) Upper panel shows a representative continuous bilateral EEG recording from a D2.B6-*Szs1* mouse alongside EMG recording. The stars indicate the occurrence of SWDs. Detail **a**: typical example of SWDs during QW. Detail **b**: typical example of isolated large-amplitude single spike during SWS. (**B**) The left panel shows a continuous EEG recording from a B6.D2-*Szs1* mouse alongside EMG recording during quiet wakefulness. The right panel corresponds to an enlargement of the traces on the left. (**C**) Overall SWDs occurrence for all strains. (**D**) SWDs occurrence during quiet wakefulness for all strains. (**E**) Intra-SWDs frequency for all strains. (**F**) SWD duration for all strains. All error bars are SD.

interactions between at least one modifier gene within *Szs1* and other genes within unlinked QTLs in regulating the occurrence of this spontaneous nonconvulsive epileptic trait. Considering the systematic involvement of the QTL-rich region on mouse distal chromosome 1 (Chr 1)—which corresponds to human Chr1q21–23—in diverse epileptic traits, our results suggest that it might contain candidate target genes of particular importance for treating diverse types of epileptic disorders as well as for understanding the epistatic interactions that determine phenotypic characteristics across syndromes.

High-resolution mapping of *Szs1* showed that of 120 genes in the introgressed congenic interval, 12 genes satisfy both criteria of being expressed in the brain and having a missense single nucleotide polymorphism (SNP) (Ferraro et al., 2004; Mozhui et al., 2008). Among this latter group, one encodes a protein involved directly in the transport of ions across cell membranes: *Kcnj10*. This gene encodes an inward-rectifier potassium ion channel Kir4.1 predominantly expressed by glial cells (Takumi et al., 1995). Homozygous *Kcnj10* knockout mice show a severe demyelinating syndrome associated with multiple neurologic defects including seizures (Djukic et al., 2007) and short life span (Kofuji et al., 2000; Neusch et al., 2001; Marcus et al., 2002).

Of interest, activity of Kir4.1 channels in astrocytes of D2 mice is reduced compared to B6 mice and this deficit is associated with an impairment in potassium and glutamate buffering (Inyushin et al., 2010). Furthermore, the Thr/Ser polymorphism in coding sequence of the (Kir4.1) at the position 262 correlates with electroshock-induced seizure susceptibility among a variety of inbred strains (Ferraro et al., 2004) and translation of these results to human epilepsy led to the discovery of an SNP at the position 271 in the *Kcnj10* protein predicting an Arg/Cys variation at amino acid position 271 in epilepsy patients with refractory mesial temporal lobe epilepsy, childhood absence, and juvenile myoclonic epilepsy (Buono et al., 2004; Lenzen et al., 2005; Heuser et al., 2010). Most recently, deleterious mutations of *Kcnj10* have been shown to be causative in the seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance (SeSAME syndrome) and epilepsy, ataxia, sensorineural deafness, and tubulopathy (EAST syndrome), which involves multiple organ systems as well as severe epilepsy as the prominent phenotype (Bockenhauer et al., 2009; Scholl et al., 2009). Taken together these results point to *Kcnj*10 as a strong candidate for a general seizure susceptibility gene, and its mutation in D2 mice might explain the results observed in the congenic animals. Definitive confirmation would arise from the analysis of SWDs in a D2 mice line with a knock-in of the allelic variant of the B6 *Kcnj10*.

Despite the compelling evidence with respect to the direct involvement of *Kcnj10* gene product, roles for SNPs in the other genes harbored by the *Szs1* locus cannot yet be ruled out. To our knowledge, except for *Pxf*, which encodes for a peroxisomal receptor and has recently been shown to be mutated in a case study of a patient with a complex clinical syndrome that include abnormal EEG and epilepsy (Mohamed et al., 2010), none of the other genes is documented to have a direct effect on cell excitability and/or seizures. However, other mechanisms might also account for the gene involvement. One particularly interesting hypothesis is that the phenotype of D2 mice results from interactions between SNPs of genes located within *Szs1* and other genes situated within and/or outside this locus. In line with this hypothesis, analysis of 18 diverse array datasets from different mouse crosses revealed that *Szs1* modulates the expression of at least 10 genes that have been implicated in seizure phenotypes including *Cacna1g*, *Scn1b,* and *Pnpo* (Mozhui et al., 2008). In every case the D2 allelic variant has a positive additive effect, increasing the expression of the transcripts by 5–20%. With respect to the control of SWD generation in D2 mice, an increase in *Cacna1g* transcripts, which underlies the expression of T-current in thalamocortical cells, is of particular significance (Kim et al., 2001). Indeed, T-current is either mutated or increased in animal models of absence seizures (Tsakiridou et al., 1995; Zhang et al., 2002, 2004; Powell et al., 2009); knock-out of *Cacna1g* prevents the occurrence of SWDs induced by gamma-Butyrolactone (GBL) administration (Kim et al., 2001) and spontaneous SWDs in some mutant mice (Song et al., 2004). Alternatively, the overexpression of this gene (37% increase in mRNA levels) is sufficient for the appearance of spontaneous SWDs (Ernst et al., 2009). Even though the increase in the expression of this gene in D2 mice compared to B6 seems small (<20%), biophysical experiments revealed that slight variations in T-type current might have major impact on the excitability of thalamocortical cells depending on the weight of their synaptic inputs (Bessaïh et al., 2008). Of interest, D2 mice have been reported to present alterations of intrathalamic inhibition (Tan et al., 2008), similar to what has been observed in other genetic rodent models of SWDs (Bessaïh et al., 2006; Cope et al., 2009; Brockhaus & Pape, 2011). No evidence for the control of genes that regulate synaptic inhibition by allelic variations within *Szs1* locus has been reported.

We propose that changes in genes within or regulated by *Szs1* such as Kcnj10 or *Cacna1g* might account for the drastic decrease of SWD occurrence in D2.B6-*Szs1* mice when compared to D2 mice. However, appearance of SWDs in B6 would necessitate concomitant abnormalities under the regulation of other loci, such as modifications of thalamocortical inhibition.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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