Infantile Spasms Is Associated with Deletion of the *MAGI2* Gene on Chromosome 7q11.23-q21.11

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Infantile spasms (IS) is the most severe and common form of epilepsy occurring in the first year of life. At least half of IS cases are idiopathic in origin, with others presumed to arise because of brain insult or malformation. Here, we identify a locus for IS by high-resolution mapping of 7q11.23-q21.1 interstitial deletions in patients. The breakpoints delineate a 500 kb interval within the *MAGI2* gene (1.4 Mb in size) that is hemizygously disrupted in 15 of 16 participants with IS or childhood epilepsy, but remains intact in 11 of 12 participants with no seizure history. *MAGI2* encodes the synaptic scaffolding protein membrane-associated guanylate kinase inverted-2 that interacts with Stargazin, a protein also associated with epilepsy in the *stargazer* mouse.

The hemizygous microdeletion of a 1.5 Mb region of chromosome 7q11.23 causes the neurodevelopmental disorder Williams-Beuren syndrome (WBS [MIM 194050]). WBS is characterized by numerous physical, cognitive, and behavioral symptoms,[1] but seizures have only rarely been reported and were presumed to be unrelated to the deletion of genes in the critical region.[2] The typical WBS deletion spans a common interval of between 26 and 28 genes, because it arises due to unequal meiotic recombination between highly similar flanking nucleotide sequences.[3] Larger WBS-associated deletions have been reported and they often have one breakpoint that is similar to those associated with the common deletion. When the deletion extends telomeric, a more severe phenotype with serious impairments in cognitive function is typically observed[4,5] and this is sometimes accompanied by infantile spasms.[6–8]

Infantile spasms (IS, also known as West syndrome) is a disorder of the developing nervous system that begins in the first year of life, most commonly between 4 and 8 months of age.[9] In approximately 50% of IS cases, the spasms are a symptom of generalized brain disturbance, including CNS infection[10] and developmental brain abnormalities such as lissencephaly (LIS1 [MIM 607432]; LISX1 [MIM 300067]), focal cortical dysplasia,[11] neurocutaneous syndromes such as tuberous sclerosis (TS [MIM 191100]) and neurofibromatosis (NF1 [MIM 162200]), incontinentia pigmenti (IP [MIM 308300]),[12,13] hypoxic ischemic encephalopathy,[14,15] or rare chromosomal or genetic abnormalities such as Down syndrome (DS [MIM 190685]), ARX mutations (ISSX1 [MIM 308350]), and CDKL5 mutations (ISSX2 [MIM 300672]).[16,17] In all these etiologies, IS is present in only a fraction of cases occurring as part of a much larger spectrum of neurological symptoms.

Idiopathic IS accounts for the other half of the cases and occurs in the absence of any brain malformation or neurological insult.[11,12,18] IS is an epilepsy syndrome with a seizure type characterized by clusters of flexion jerks of the neck, trunk, and extremities lasting 1–2 s occurring throughout the day. These spasms have a distinctive high-voltage, disorganized pattern on electroencephalogram (EEG), called hypsarrhythmia, that is seen (in some form) in approximately two thirds of cases of IS.[19] IS is associated with a significant risk of mortality and morbidity,[20] and is usually treated with adrenocorticotropic hormone or Vigabatrin, both of which are variably effective and can have severe side effects.[21] The characteristic hypsarrhythmia pattern must be abolished if the prognosis is to be improved, otherwise the immature brain appears to

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Table 1. Summary of Clinical Features in Participants with Deletions of Chromosome 7q11.23-q21.1

Case	Ref.	Gender	Deletion Size (Mb)	Breakpoint Mapping	Clinical Description
1	TS	M	3.4	Array, QPCR	WBS with severe hypercalcemia
2,3,4	5	2M, 1F	2.4	FISH	WBS with moderate MR (ref 5 cases 15481, 18393, 18317)
5	5/TS	F	4.2	Array	WBS with severe MR (ref 5 case 23162)
6	TS	M	4.2	Array	WBS with severe MR
7	5/TS	F	4.3	QPCR	WBS with severe MR (ref 5 case 29948)
8	4/TS	F	4.2	Array	WBS with periventricular heterotopia, severe MR, nonverbal
9	28	F	2.4–2.8	QPCR	WBS cognitive-behavioral profile with moderate MR and autism spectrum disorder
10	7/TS	M	4.4	Array, QPCR	WBS with IS (variation form of hypsarrhythmia), severe developmental delay
11	TS	F	6.7	QPCR	WBS with IS (hypsarrhythmia) at 4 months and severe global developmental delay
12	TS	M	5.5	QPCR	WBS with severe delays, IS, myoclonic, and tonic seizures
13	TS	M	11–12.5	QPCR	WBS with IS, hypotonia, severe PMD, nonverbal, Wolff-Parkinson-White syndrome
14	TS	F	10	QPCR	WBS with IS, hypoglycemia, contractures, severe PMD
15	TS	M	8.3	Array, QPCR	WBS with IS and focal seizures at 5 months, severe MR
16	5/TS	M	11	Array	WBS with IS, severe MR (ref 5 case 20495)
17	6/TS	M	17	Array, QPCR	WBS with IS (hypsarrhythmia) at 2 months and severely retarded PMD
18	TS	M	19.6	Array, QPCR	WBS with EEG abnormalities, severe PMD, marked hypotonia
19	8	F	>9	MMA	WBS with petit mal seizures, macrocephaly, severe MR, and minimal speech
20	TS	F	17	Array, QPCR	WBS with IS, minimal development and blindness
21	TS	M	26	QPCR	IS, childhood epilepsy, optic nerve hypoplasia, cerebral palsy, severe MR, nonverbal
22	TS	M	11.5	Array, QPCR	Myoclonus epilepsy, developmental delay, nonverbal
23	27	F	16	MMA	IS, PMD, and dysmorphism
24	TS	F	15–20	MMA	Seizure disorder age 7 years, nonverbal
25	30/TS	F	19	Array, QPCR	IS, severe MR, microcephaly, scoliosis, dysmorphism, and ectrodactyly
26	29/TS	F	3	Array, QPCR	Growth retardation, MR, clinodactyly, mild spasticity, hypersensitivity to noise
27	26	F	16	Array	Growth retardation, severe MR, microcephaly, complete hearing loss
28	25	M	12–14	FISH	Microcephaly, short stature, myoclonus-dystonia syndrome (e-sarcoglycan deletion), developmental delay

Abbreviations: TS, this study; WBS, Williams-Beuren syndrome; MR, mental retardation; PMD, psychomotor delay; IS, infantile spasms; ns, not specified; M, male, F, female; Array, Affymetrix Human Mapping 500K or Genome-Wide Human SNP 6.0 Arrays; FISH, fluorescent in situ hybridization; QPCR, quantitative real-time PCR; MMA, microsatellite marker analysis.
Cases 10–25 indicate a diagnosis of infantile spasms or other seizure disorder.

remain hyperexcitable and proper neurodevelopment is impeded. Approximately 50%–60% of children with IS will go on to develop other seizure types.[22,23]

Reports of larger hemizygous chromosome deletions associated with both WBS and IS suggested that a locus for IS existed within band q11.23-q21.1 of chromosome 7, distal to the region commonly deleted in WBS.[6–8] In order to determine whether a novel locus for IS could be defined, we identified 12 cases with interstitial deletions of 7q11.23-q21 from our Chromosome 7 Annotation Project clinical database[24] and another 16 cases from the literature with deletions overlapping this same region.[4–8,25–30] DNA samples were available from the 12 new cases and from eight of the cases from the literature.

In 12 cases where the availability of DNA and array technology allowed, we mapped the deletion boundaries by using comparative intensity analysis with single nucleotide polymorphism (SNP) microarrays. For the remaining 8 cases with DNA available, deletion breakpoints were mapped by other methods (outlined in Table 1). The breakpoints of cases from the literature where no DNA sample was available were determined from the published data. All protocols were approved by the Research Ethics Boards of the institutions involved, and appropriate informed consent was obtained from all human participants or their guardians. For all participants, genomic DNA was prepared from peripheral blood lymphocytes by standard methodologies. Clinical descriptions of 16 cases have been published previously.[4–8,25–30] Additional cases described in this study included two with a diagnosis of WBS, seven with a diagnosis of WBS plus IS, and three with a diagnosis of IS or other seizure disorder without WBS. Clinical data for all subjects with hemizygous 7q11.23-q21.1 deletions are presented in Table 1.

To further define the breakpoints of the interstitial 7q11.23-q21.1 deletions and to establish copy number variation (CNV) content in the rest of the genome, 12 of the 28 cases were genotyped with either Affymetrix Human Mapping 500K or Genome-Wide Human SNP 6.0 Arrays (Affymetrix Inc., Santa Clara, CA) according to the manufacturer's instructions. CNV analysis of Affymetrix 500K arrays was performed as described previously.[31] Affymetrix 6.0 arrays were analyzed for CNV with a combination of Partek Genomics Suite (Partek Inc., St Louis, MO) and Affymetrix Genotyping Console (Affymetrix Inc.).

The CNVs identified in each DNA sample were compared with previously documented CNVs found in 1652 healthy population controls[31] and those in the Database of Genomic Variants, a curated catalog of structural variations in the human genome.[32] All identified CNVs are presented

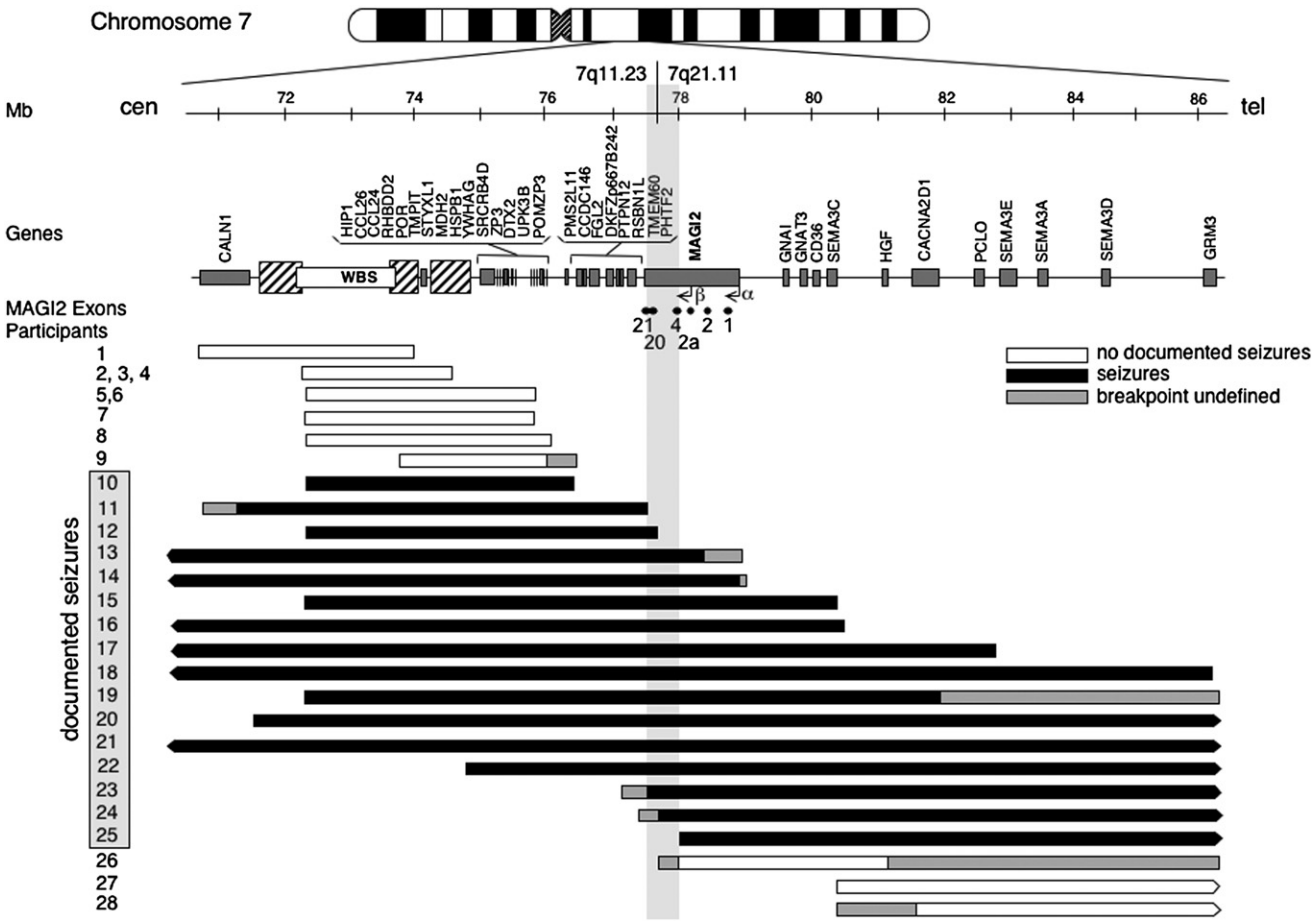

Figure 1. Summary of Interstitial Deletions of 7q11.23-q21.1 in Cases with and without Infantile Spasms

Deletion mapping of cases 1 to 28 defines a critical region for infantile spasms (IS) spanning part of *MAGI2*. Quantitative real-time PCR amplimers are indicated below the *MAGI2* gene along with the two known transcriptional start sites for the α and β isoforms of the protein. *MAGI2* is partially or wholly deleted in 12 cases with IS, and another three with childhood epilepsy (cases 11–25). Cases 1–9 and 27–28 have interstitial deletions that are proximal and distal, respectively, to *MAGI2* and have had no diagnosis of epilepsy. Case 10 has a diagnosis of IS but is not deleted for *MAGI2*. Case 26 is deleted for part of *MAGI2* but has not had any diagnosis of epilepsy.

Chromosome deletions are represented by bars, below a map of genes from the 7q11.23-q21.11 region. Black bars represent deletions in cases with documented seizures, and white bars represent deletions in cases without documented seizures. Grey bars indicate breakpoints that have not been refined.

in Table S1 available online. Comparative intensity analysis enabled the mapping of the 7q11.23-q21.1 deletion boundaries in each sample, to within approximately 10 Kb. When a deletion breakpoint lay within the low copy repeats flanking the WBS region, it was impossible to determine the breakpoint location because of the presence of multiple copies of SNPs from within these low copy repeats.

Confirmation of the array data and refining of the breakpoints within and around *MAGI2* was carried out by quantitative real-time PCR analysis with the 7900HT genetic analyzer (Applied Biosystems, Foster City, CA). The total volume was 11 μl and reactions were performed in triplicate, with 5 ng of template for 40 cycles of amplification via Power SYBR master mix (Applied Biosystems). The DNA copy number of each test sequence was obtained from a calibration curve that assumes the reference genome is present in two copies at that site. Genomic ratios were determined by comparing absolute copy number of the test sequences to the reference gene HMBS. Primer positions are shown in Figure 1 and primer sequences in Table S2. Quantitative real-time PCR analysis of *MAGI2* exon 1 and exon 21 was carried out on all available DNA samples (cases 1, 5–8, 10–18, 20–22, 24–26), and breakpoints for critical cases were further refined with additional primer pairs (Tables S2 and S3).

We found deletions of 7q11.23-q21.1 ranging from 2.4 Mb to more than 25 Mb in size (Figure 1 and Table 1). Seizure history was obtained for all cases and genotype-phenotype correlation was performed on the basis of the presence or absence of IS or other forms of seizure activity. We defined a smallest region of overlap associated with IS of approximately 500 kb, spanning part of the 1.4 Mb membrane-associated guanylate kinase inverted-2 gene (*MAGI2* [MIM 606382]). All but one of 16 individuals with a chromosome

7 deletion and IS were missing all or part of *MAGI2*, whereas only one of 11 individuals with a chromosome 7 deletion and no seizure history was missing any part of *MAGI2* ($p < 0.001$; chi square, 1 df). There are no reported CNVs that span exons of *MAGI2*, further supporting the hypothesis that hemizygosity for this gene results in a phenotypic effect.[32] Based on the available evidence, we propose *MAGI2* as a dominant locus for IS.

All the cases with IS had deletions spanning multiple genes, suggesting that IS could arise as the consequence of haploinsufficiency for more than one gene, or alternatively as a result of position effects mediated by the large chromosomal deletions. However, the range of deletion sizes and the location of the deletions themselves argue against these hypotheses. The deletions that include *MAGI2* extend either distal or proximal to the gene. Although some deletions extend in both directions, there are several deletions that extend in opposite directions so that they include completely different gene sets (Figure 1; cases 11–14 versus cases 23–25), making a two-gene hypothesis extremely unlikely. The effect of the deletion itself also seems an unlikely explanation for IS, because there are individuals who have large deletions outside the critical interval but do not exhibit seizures or associated phenotypes (Figure 1; cases 1–9, 27, 28).

Only a single participant with WBS and well-documented IS harbored a deletion that did not span any part of *MAGI2* (case 10).[7] However, because the etiology of IS is heterogeneous, it is possible that the IS in this individual is unrelated to their chromosome 7 deletion, particularly because their deletion is very similar to five other cases without IS (Figure 1; cases 5–9). Array analysis did not reveal any previously unreported copy number variant that could have contributed to the phenotype in this individual (Table S1). In addition, a single case harbored a deletion that encompassed part of *MAGI2*, without a documented occurrence of IS (case 26).[29] This woman carries a 3 Mb de novo deletion and was referred for genetic testing at the age of 10.5 years because of nonspecific mental retardation. Although she has had no documented seizure activity since the age of 10.5 years, her early clinical history was not available so we cannot exclude the possibility that she may have had earlier episodes of epilepsy or IS.

MAGI2 (also known as S-SCAM, synaptic scaffolding molecule) was originally characterized as a scaffold protein interacting with N-methyl-D-aspartic acid (NMDA) receptors at excitatory synapses in the brain, its predominant site of expression,[33] but has since been shown to interact with many different proteins pre- and postsynaptically and at both excitatory and inhibitory synapses.[34] Perhaps the most intriguing interaction of MAGI2 is that with stargazin,[34] the protein mutated in the *stargazer* mouse, one of the first and best characterized mouse models of epilepsy.[35] *stargazer* mice have impaired α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor transport through the endoplasmic reticulum and *cis*-Golgi compartments and lack functional AMPA receptors.[36]

MAGI2 comprises a guanylate kinase domain, two WW domains, and five PDZ domains. At least two isoforms have been identified in humans, the largest (α) with an additional N-terminal PDZ domain, and the other (β) with a transcriptional start site in the alternative exon 2a.[37] A recent mouse model lacking the longest, α isoform of MAGI2 exhibited no obvious phenotype in the heterozygous state, and homozygous mutants died at birth;[38] however, the MAGI2 β isoform was intact in these mice and every one of the documented protein interactions occurs via domains shared by both isoforms. All of the individuals with IS and disruption of *MAGI2* reported in the present study (cases 11–25) had deletions that would result in the hemizygous disruption of both isoforms of the protein, suggesting that IS results from a decrease in protein interactions involving the common domains of MAGI2, i.e., the WW domains and/or the five PDZ domains.

The identification of this locus for IS has implications for the clinical management of individuals with WBS and large deletions of 7q11.23-q21.1. Infants with WBS who have deletions that extend to *MAGI2* present with additional clinical features to those found in individuals with the classic deletion (Table 1). These children exhibit very delayed motor and developmental milestones compared to children with typical WBS, often in combination with hypotonia and severe intellectual disability. Their prognosis is also complicated by the presence of IS that may further impact upon their neurological development. A longitudinal study of the outcome of these individuals would determine the extent and severity of their developmental impairment and help to establish some prognostic guidelines for other families of newly diagnosed children with similar deletions.

Although approximately 40% of human epilepsy is estimated to be genetically determined,[39] only a small fraction of causative genes have been identified and almost all in families exhibiting rare forms of epilepsy inherited in a Mendelian fashion. To date, practically all these known genes code for ion channels.[40] The identification of hemizygosity for the postsynaptic scaffolding protein MAGI2 as a cause of IS sheds new light on the genetic etiology of epilepsy and suggests that other proteins that regulate the trafficking, distribution, or function of the glutamate receptors are attractive candidates for involvement in human epilepsy. The postsynaptic density is comprised of more than 100 proteins, offering numerous avenues by which to disrupt the proper function of the synapse. Further research will be needed to establish exactly how *MAGI2* hemizygosity leads to IS and whether the spasms are truly idiopathic when associated with MAGI2 gene mutations rather than interstitial chromosome deletions. The identification of a causative gene should allow the development of a genetic mouse model of IS and eventually lead to the development and testing of targeted, effective medications for this severe epilepsy, both in its isolated form and in children with WBS.

Supplemental Data

Three tables are available at http://www.ajhg.org/.

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Web Resources

The URLs for data presented herein are as follows:

Database of Genome Variants, http://projects.tcag.ca/variation/
Chromosome 7 Annotation Project, http://www.chr7.org/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

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