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RESEARCH ARTICLE

A genetic locus for sensory epilepsy precipitated by contact with hot water maps to chromosome 9p24.3-p23

KALPITA R. KARAN[1], PARTHASARTHY SATISHCHANDRA[2], SANJIB SINHA[2] and ANURANJAN ANAND[1,3]*

[1] *Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bengaluru 560 064, India*
[2] *Department of Neurology, National Institute of Mental Health and Neurosciences, Bengaluru 560 029, India*
[3] *Neuroscience Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bengaluru 560 064, India*
*For correspondence. E-mail: anand@jncasr.ac.in.

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Abstract. Hot water epilepsy (HWE) is a rare form of sensory epilepsy where seizures are precipitated by a stimulus of contact with hot water. While earlier studies have suggested causal role of genes for HWE, specific underpinnings are beginning to be explored only recently. We carried out a whole genome-based linkage analysis in a family where most of its members affected by HWE and found evidence of a previously unknown locus at chromosome 9p24.3-p23. Parametric two-point analysis suggested linkage with the greatest LOD score of 3.42 for the marker D9S286 at 9p24.1 at recombination fraction (θ) = 0, 90% penetrance value and 1% phenocopy rate. The highest multipoint LOD score of 3.42 was obtained for same marker at 9p24. The critical genetic interval of about 10 Mb of DNA was defined by the markers D9S917 and D9S168 corresponding to the centromere-distal and centromere-proximal recombination boundaries, respectively. This observation along with our previous findings of hot water genetic loci at 10q21.3-q22.3 (OMIM: 613339) and 4q24-q28 (OMIM: 613340), indicates unanticipated genetic heterogeneity for the disorder in families from a relatively small geographic region in the southern parts of India.

Keywords. sensory epilepsy; seizures; genetic heterogeneity; linkage mapping.

Introduction

Sensory or reflex epilepsies are a group of epilepsy syndromes where seizures are triggered due to external stimuli. Apparently, many simple stimuli like light, sound or relatively complex ones, like reading, writing, solving arithmetic problems can provoke seizures. Individuals with sensory epilepsies develop seizures in response to specific stimuli and usually do not suffer from spontaneous seizures. These epilepsies are intriguing neurobehavioural phenotypes involving a rapid transition from apparently normal functioning brain to an epileptic brain, upon provocation by a specific stimuli. A rather unusual form of sensory epilepsy triggers by contact with hot water, was first described in a 10-year-old boy from New Zealand, manifesting episodes of staring expression, stiffened extremities, and loss of consciousness, whenever he was given a bath (Allen 1945). Subsequently, the cases of hot water epilepsy have been reported from Australia (Keipert 1969), USA (Stensman and Ursing 1971), Canada (Szymonowicz and Meloff 1978), UK (Moran 1976), Japan (Morimoto *et al.* 1985) and Turkey (Bebek *et al.* 2001). However, it is in India that this disorder is most prevalent. Hot water epilepsy has been variously described as bathing epilepsy (Shaw *et al.* 1988; Lenoir *et al.* 1989) and water immersion epilepsy (Mofenson *et al.* 1965). In India, the first reported case of HWE was of an 11-year-old boy displaying troubled behaviour in the background of impaired consciousness during hot water bathing (Mani *et al.* 1968). During subsequent years, additional 210 cases were reported manifesting similar behavioural and clinical features while bathing in hot water (Mani *et al.* 1968; 1974). After almost over a decade of these early reports, Satishchandra and colleagues published a detailed report comprising 279 HWE cases accounting for about 4% of epilepsy patients in

south India (Satishchandra *et al*. 1988). The mean age of onset of HWE is 13±11 years and in about 60% of the patients the first episode is seen before the age of 10 years (Satishchandra *et al*. 1988; Bebek *et al*. 2001). Seizures in HWE are of focal origin. At the onset of a seizure, the patient is characterized by a dazed look, sense of fear, irrelevant speech, complex automatisms and hallucinations of visual and auditory type. In about one-third of HWE patients, manifestation of generalized tonic–clonic seizures (GTCS) is reported. HWE patients have no neurological deficit and interictal EEG is usually normal. In about 20% of the patients diffused EEG abnormalities were observed (Mani *et al*. 1974). Ictal EEG recordings are technically difficult to obtain. However, a few investigators have reported focal activity in the temporal and frontal lobes of the brain during the ictus (Shaw *et al*. 1988; Morimoto *et al*. 1985). Familial clustering in HWE and positive family histories in Indian and Turkish patients have suggested genetic component to the aetiology of this disorder (Mani *et al*. 1974; Bebek *et al*. 2001; Satishchandra 2003). Previous studies from our laboratory have found two HWE loci at chromosomes 10q21.3-q22.3 (Ratnapriya *et al*. 2009a) and 4q24-q28 (Ratnapriya *et al*. 2009b). Here, we present results of a genetic linkage study which suggests that there is a locus at chromosome 9p24.3-p23, in a hot water epilepsy family.

Subjects and methods

Family ascertainment and clinical characterization

We ascertained a hot water epilepsy family, family 300 (figure 1) with seven of its members affected with the disorder, one clinically asymptomatic and nine unaffected members from the Department of Neurology, National Institute of Mental Health and Neurosciences. This family was recruited through proband III:4, who was diagnosed with HWE at the age of 34 years. His interictal EEG showed generalized discharges arising from the left temporal region of the brain. He was treated with intermittent prophylactic clobazam therapy. HWE in family-300 is transmitted in an autosomal dominant mode with incomplete penetrance. All individuals with HWE satisfied the clinical inclusion criteria of seizures precipitated by hot water: hot water at 40−42°C poured over the head was sufficient to precipitate seizures. Information regarding the age-of-onset, type of seizures, timing of seizures in relation to hot water bath, histories of febrile seizures, development of nonreflex seizures in the HWE patients and family histories of epilepsy were obtained from patients and their surrogate respondents who had witnessed multiple seizure episodes in the members. A 10-mL blood sample was collected from all participating members of the family. DNA was isolated from peripheral white blood cells using a standard method (Sambrook and Russell 2001).

Genomewide linkage mapping

For family-300, a whole genome-based linkage analysis was carried out using the ABI Prism MD-10 linkage mapping panel v2.5 MD10 (Applied Biosystems, Foster City, USA) comprising 382 microsatellite markers spaced over the genome at an average resolution of 10 centiMorgans (cM). The marker order and intermarker distances were obtained from the Genethon and deCODE human linkage maps (Dib *et al*. 1996; Kong *et al*. 2002). All markers were amplified and pooled using conditions as per Applied Biosystems user's manual protocols. Individual DNA samples were arrayed in 96-well microtiter plates and subjected to amplification by PCR. Polymerase chain reactions were performed in a GeneAmp 9700 thermocycler (Applied Biosystems). Pooled amplified products were mixed with a cocktail of Hi-Di formamide (Applied Biosystems) and LIZ-500 internal size standard (Applied Biosystems) and denatured at 95°C for 5 min. The products were loaded onto an ABI3730 Genetic Analyzer (Applied Biosystems) for electrophoresis. The output data were analysed for fragment sizing using Genescan 3.7 (Applied Biosystems) followed by allele calling by Genotyper 3.7 (Applied Biosystems). In addition, a reference individual, CEPH 1347-02, with known genotype was loaded for each marker as a positive control.

For fine mapping in the 9p24-p23 region, 11 additional microsatellite markers (D9S1779, D9S917, D9S1858, D9S54, D9S1813, D9S1810, D9S1849, D9S2156, D9S168, D9S268 and D9S1869) encompassing the region were analysed to confirm the linkage and refine the recombination boundaries to delimit the critical genomic interval. These additional markers spanned the chromosomal region of about 33 cM interval (0–33.5 cM) at an average genetic resolution of 2.1 cM. The PCR for each marker was carried out in a 10 μL volume containing 50 ng of genomic DNA, 2.5 pmol of each primer, 200 μM of each dNTP, 50 mM KCl, 10 mM Tris-HCl (pH 8.4), 1.5 mM $MgCl_2$ and 0.5 U of *Taq* polymerase (Invitrogen). PCR amplifications were performed using GeneAmp 9700 (Applied Biosystems) at the following conditions: initial denaturation at 94°C for 5 min, followed by 40 cycles of denaturation at 94°C for 30 s, annealing at 54−60°C for 30 s, extension at 72°C for 30 s and a final extension at 72°C for 10 min.

Statistical analysis

Parametric two-point LOD scores were calculated using MLINK of LINKAGE 5.2, considering autosomal dominant inheritance with 60–90% penetrance values, 1% phenocopy, disease allele frequency of 0.0001 and no difference in male and female recombination rates (Lathrop *et al*. 1984). Allele frequencies for all the markers were determined from the data available for the family. Multipoint parametric analyses were done using GeneHunter

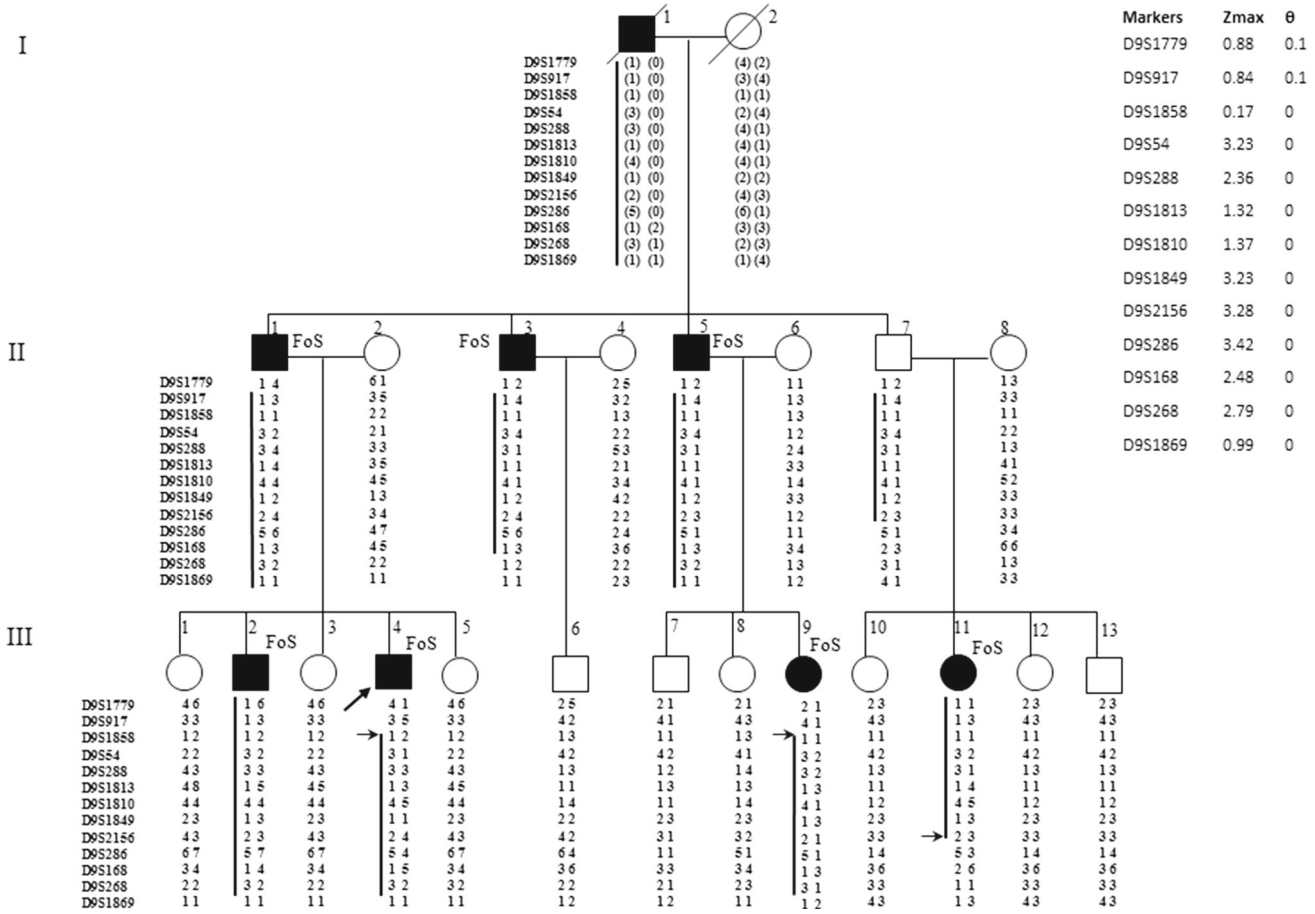

Figure 1. Pedigree of family-300. The filled symbol represents affected individual and an empty symbol represents unaffected individual. FoS (focal seizures with altered awareness) is the type of seizures observed in the affected individuals. Roman numbers to the left of the pedigree denote generations and Arabic numbers beside the symbols denote individuals. A 13-marker haplotype is indicated below the symbols. Alleles in parentheses were inferred. Key recombination events, in individuals, III:4 and III:11, are marked as arrows. The maximum LOD scores (Zmax) obtained with the markers on the haplotype are shown.

2.1 (Kruglyak *et al*. 1996). Haplotypes were constructed manually in the order of the decode linkage map based on genotyping data and were inferred maintaining a minimum number of intermarker recombination events. These haplotypes were also confirmed with those generated using MaxProb in GeneHunter 2.1 (Kruglyak *et al*. 1996). Manual haplotyping was done to identify the shared genomic regions among affected individuals in the family, define the recombination boundaries and to search for genotyping errors, if any.

Results

In the genomewide linkage analysis of family-300, the highest two-point LOD score obtained was 3.42 for the marker D9S286 at 9p24.3-p23, at recombination faction (θ) = 0, for genetic parameters of dominant inheritance pattern, penetrance value of 90% and 1% phenocopy rate (figure 1; table 1). Eleven additional fine mapping markers situated at locations flanking the panel microsatellite markers provided significant LOD scores calculated under the same genetic parameters (table 1). This strengthened our evidence for linkage at the 9p24.3 region. At no other marker analysed, a LOD score that could be considered suggestive of linkage was obtained. The next highest LOD score observed in this analysis was 1.34, at θ=0, for D13S158 on chromosome 13q33. Two markers, D13S159 and D13S173, flanking D13S158, provided LOD score of −1.42 and −0.72, respectively. Multipoint parametric LOD score analysis was performed using GeneHunter 2.1. The highest multipoint LOD score obtained was 3.36, for D9S54, D9S288, and D9S1813 at 9p24 (figure 2).

Haplotypes were constructed manually by considering minimum number of recombination events and were also compared with the ones generated using MaxProb, GeneHunter 2.1 (Kruglyak *et al*. 1996). All the affected members shared a 13-marker haplotype delimited by D9S917 and D9S168. A recombination event between D9S917 and D9S1858 in the affected individuals III:4 and III:9 defined the centromere-distal boundary. The centromere-proximal boundary was defined by recombination between D9S286 and D9S168 in the affected individual III:11.

Table 1. Two-point LOD scores for markers at chromosome 9.

DNA markers	θ=0	θ=0.1	θ=0.2	θ=0.3	θ=0.4
D9S1779	−0.52	0.88	0.82	0.52	0.17
D9S917#	−0.56	0.84	0.79	0.50	0.17
D9S1858	0.17	0.12	0.07	0.03	0.01
D9S54	3.28	2.62	1.92	1.20	0.46
D9S288	2.36	1.91	1.42	0.89	0.33
D9S1849	3.30	2.64	1.94	1.21	0.48
D9S2156	3.28	2.62	1.92	1.20	0.46
D9S286	3.42	2.74	2.01	1.24	0.48
D9S144	2.79	2.26	1.70	1.09	0.48
D9S168#	2.48	1.99	1.49	0.93	0.43
*D9S*1869	0.99	0.74	0.48	0.25	0.07
D9S285	−2.25	0.60	0.66	0.49	0.20
D9S157	−3.58	−0.31	0.08	0.15	0.07
D9S171	−0.24	−0.15	−0.01	0.03	0.01
D9S161	−2.40	−0.81	−0.27	−0.07	−0.01
D9S1817	−3.04	−1.01	−0.34	−0.07	0.00
D9S273	1.04	0.77	0.50	0.26	0.07
D9S175	−0.08	0.38	0.33	0.20	0.06
D9S167	−2.15	−0.96	−0.42	−0.16	−0.04
D9S283	0.31	0.22	0.14	0.07	0.02
D9S287	−1.92	−0.56	−0.20	−0.05	0.00
D9S1690	−1.81	−0.47	−0.12	0.00	0.01
D9S1677	−2.15	−0.62	−0.23	−0.07	−0.02
D9S1776	−2.04	−0.43	−0.06	0.03	0.01
D9S1682	−3.30	−0.91	−0.45	−0.18	−0.04
D9S290	−3.35	−1.07	−0.53	−0.21	−0.05
D9S164	−2.05	−1.13	−0.64	−0.26	−0.06
D9S1826	−2.99	−1.06	−0.34	−0.05	0.01
D9S158	0.51	0.41	0.28	0.14	0.04

Parametric two-point LOD scores obtained for the chromosome 9 markers in family-300. Parametric two-point LOD scores were calculated using MLINK of LINKAGE 5.2, considering autosomal dominant inheritance with 90% penetrance value, 1% phenocopy, disease allele frequency of 0.0001 and no difference in male and female recombination rates (Lathrop *et al.* 1984). Allele frequencies for the markers were determined from the data available from the family. #Represents markers which define the recombination boundaries. Fine mapping markers flanking D9S288 and D9S286 are shown in italics.

The critical region, between these recombination boundaries, corresponds to a genetic interval of 23.2 cM and a physical length of 10.1 Mb (Human Genome Map Viewer Build 37.1 database at NCBI, http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi?taxid=9606). The haplotype encompassing D13S158 was found not to cosegregate with the clinical phenotype in the family and therefore, this region was not pursued further. Two known loci for hot water epilepsy at chromosomes 10q21-q22 (Ratnapriya *et al.* 2009a) and 4q24-q28 (Ratnapriya *et al.* 2009b) were excluded in the present genetic mapping experiments. In family-300, the highest two-point LOD scores at the 10q21-q22 region was 0.25 for D10S192; and for the 4q24-q28 region was 0.33 for D4S1535. Haplotype analysis of these two regions supported the LOD score analysis excluding 10q21-q22 and 4q24-q28 regions as potentially disease-associated intervals in family-300.

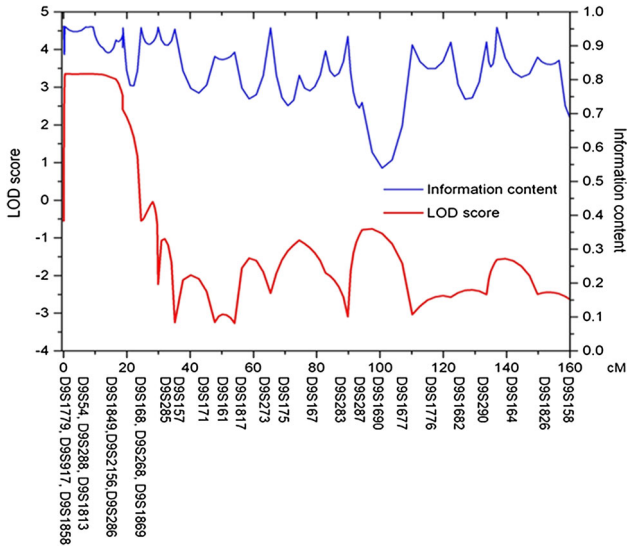

Figure 2. Multipoint genetic analysis of chromosome 9 region. The *x*-axis shows genetic length and the markers of the chromosome 9 subregion. The *Y-axis* (*left*) shows LOD scores (red line) and *y*-axis (right), information content (blue line) for the markers.

The critical region harbours ~60 protein coding genes (table 2), of which 19 are expressed in the brain. While there are likely to additional genes which are uncharacterized in the region, certain potential candidate genes based on their known expression and functional relevance are: *KANK1*, involved in establishing cell-polarity and neurite outgrowth; *KCNV2*, for voltage-gated potassium channel activity; *SLC1A1*, for clearing of glutamate from synaptic cleft and neurotransmission and *PTPRD* known to facilitate neuronal differentiation.

Discussion

In this report, we have described genetic linkage analysis of a three-generation family with its members affected with hot water epilepsy, from the state of Karnataka, India. This work identifies a previously unknown genetic locus linked to hot water epilepsy at chromosome 9p24.3-p23. A study comprising sequence analysis of this locus and functional analysis of the associated variants in cultured mammalian cells has been published elsewhere (Karan *et al.* 2017). Additional epilepsy loci known to map to chromosome 9 are (figure 3): EIG3 for epilepsy, idiopathic generalized susceptibility three at 9q32-q33 and epolm for epilepsy, occipitotemporal lobe, and migraine with aura at 9q21-q22. EIG3 was reported by Baykan and colleagues in a Turkish family (Baykan *et al.* 2004) and epolm was identified in a Belgian family (Deprez *et al.* 2007). The highest LOD score in family-300 was obtained in a genetic model comprising penetrance value of the causative allele to be about 90%. It may be noted that individual II-7 is an

Table 2. Certain brain-expressed potential candidate genes for HWE in the 9p24.3-p23 locus (GenBank; GenBank sequence database at NCBI, NIH, USA).

Marker	Gene symbol	Physical location	Description
D9S917		434455–434588	
	ANKRD15	494703–736103	Ankyrin repeat domain 15
	DMRT1	831690–959090	Double sex and mab-3 related transcription factor 1
	DMRT3	966964–981732	Double sex and mab-3 related transcription factor 3
	DMRT2	1040601–1047552	Double sex and mab-3 related transcription factor 2
	SMARCA2	2005342–2183624	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2
	VLDLR	2611793–2644485	Very low density lipoprotein receptor
	KCNV2	2707526–2719757	Potassium channel, subfamily V, member 2
	KIAA0020	2794152–2834130	Pumilio domain-containing protein KIAA0020
	RFX3	3214645–3515983	Regulatory factor X, 3
	GLIS3	3814128–4290035	GLIS family zinc finger 3
	SLC1A1	4480444–4577469	Solute carrier family 1(neuronal/epithelial high affinity glutamate transporter system Xag), member 1
	PPAPDC2	4652298–4655262	Phosphatidic acid phosphatase type 2 domain containing 2
	CDC37L1	4669566–4696594	Cell division cycle 37 homolog (*Saccharamyces cerevisiae*)-like 1
	AK3	4701158–4731227	Adenylate kinase 3
	RCL1	4782834–4851064	RNA terminal phosphate cyclase-like 1
	JAK2	4975245–5117995	Janus kinase 2 (a protein tyrosine kinase)
	PDCD1LG2	5500570–5560398	Programmed cell death 1 ligand 2
	ERMP1	5774572–5823081	Endoplasmic reticulum metallopeptidase 1
	RANBP6	6001019–6005618	RAN binding protein 6
	UHRF2	6403151–6497051	Ubiquitin-like, containing PHD and RING finger domains, 2
	GLDC	6522464–6635692	Glycine dehydrogenase (decarboxylating)
	JMJD2C	6747654–7165648	Jumonji domain containing 2C
	PTPRD	8304246–10602509	Protein tyrosine phosphatase, receptor type, D
D9S168		10588255–10588483	

asymptomatic carrier transmitting the linked haplotype to III-11, but not manifesting any of the clinical features of hot water epilepsy. We are unable to understand any specific reason behind low penetrance. This is likely to involve complex interplay between the potentially causative gene and genetic, and environmental modifiers of the phenotype.

While the first case of hot water-induced sensory epilepsy was reported over 70 years ago (Allen 1945), genetic studies to examine its molecular basis are being embarked on in the last 10 years or so. It has been proposed that HWE is precipitated by complex tactile and temperature stimuli (Stensman and Ursing 1971) with tactile stimuli playing an important role in triggering of seizures and temperature providing an additive effect over somatosensory stimulation. The manner in which HWE is triggered finds an interesting correlation with a common cultural custom and life style in certain parts of India, which involves hot water bathing with application of warm oil on the head. Episodes of HWE are usually precipitated following this bathing ritual. In India, the mean age of onset for HWE is much higher than that observed among nonIndian patients. About 62% of non-Indian patients precipitate seizures upon immersion in hot water (Ioos *et al*. 1999). Although structural lesions were not detected through a routine MRI, SPECT scanning in cases of HWE have highlighted ictal hypermetabolic state in medial temporal lobe and hypothalamic areas with an eventual spread to opposite areas in brain (Satishchandra 2003). These observations suggest activation of specific anatomical regions and their function in the evolution of the seizures.

Hot water bath triggering reflex epilepsy and high fever leading to febrile convulsions (FC) in children suggest apparently similar mechanisms. While among the families we have examined to date, the affected members mani-

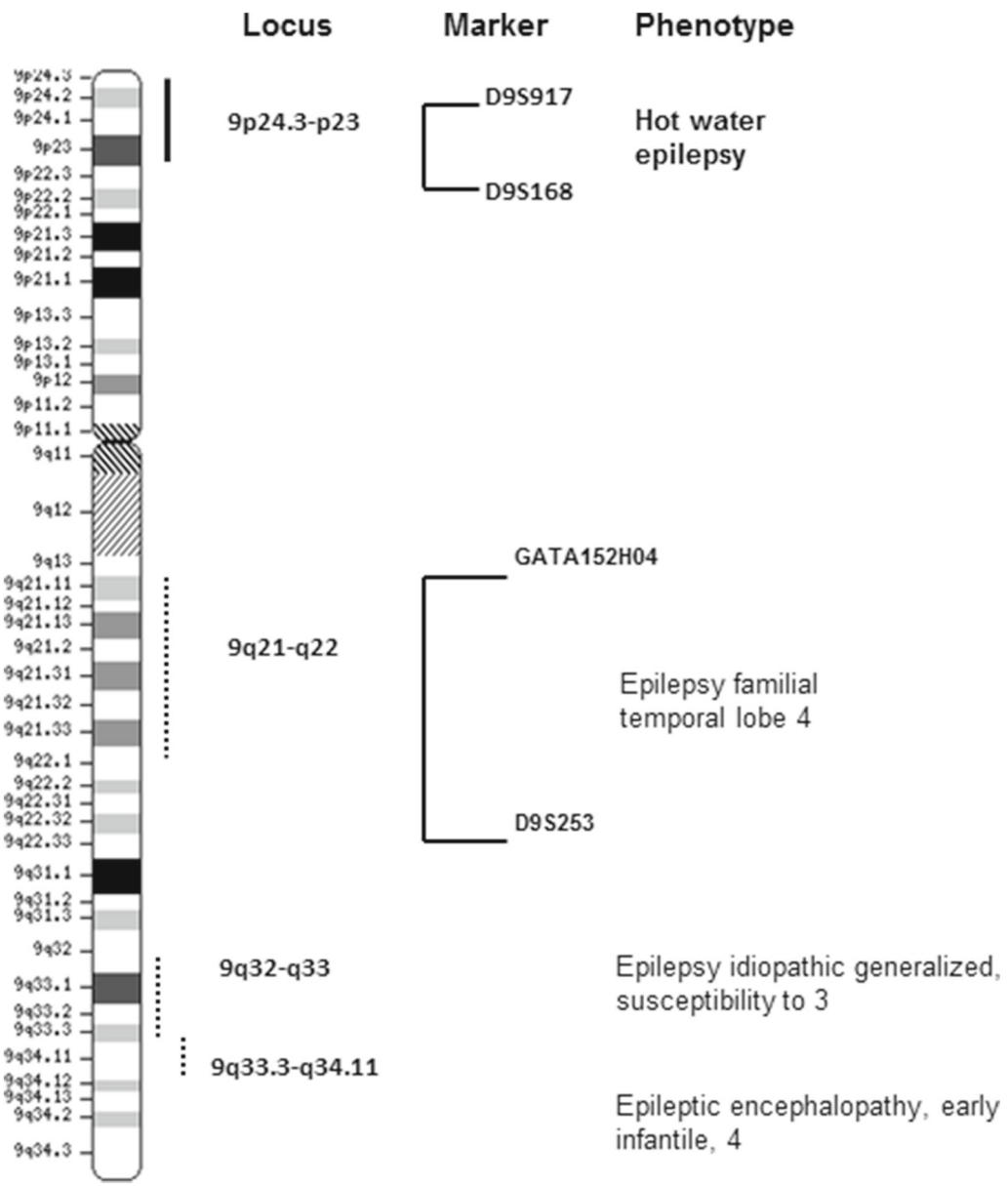

Figure 3. Schematic representation of chromosome 9, showing relative locations of the hot water epilepsy locus (solid line) identified in this study and previously known epilepsy genetic loci (dashed lines). Physical map and markers of the chromosome are based on the Human Genome Map Viewer Build 37.3 database, NCBI.

fested hot water epilepsy without a history of FC, about 5% of HWE patients do manifest FC during childhood prior to the development of seizures precipitated by hot water bath (Satishchandra *et al*. 1988). Genetic loci for familial FC have been mapped to chromosomes 2q23-q24, 3p24.2-p23, 5q14-q15, 5q31.1-q33.1, 6q22-q24, 8q13-q21, 18p11.2, 19p13 and 22q22 (Audenaert *et al*. 2006). However, the loci identified for HWE in this or other studies are different from the loci implicated in FC.

Animal models may be a key to our cellular and molecular understanding of temperature-generated seizure phenotype. An interesting phenomenon of hyperthermic kindling was observed in wistar rats repeatedly exposed to hot water at 45°C (Klauenberg and Sparber 1984; Jiang *et al*. 1999). Histological analysis of the brain of these animals revealed hippocampal mossy fibre sprouting following hyperthermic stimulation. Seizure-like electrophysiological discharges have been recorded in the hippocampus of such kindled rats (Ullal *et al*. 1996). Satishchandra and colleagues have proposed that a phenomenon similar to hyperthermic kindling could be one of the reasons for the development of HWE in humans (Satishchandra *et al*. 1988). Other than humans, mutations in the *shaker and Nubian* genes in *Drosophila* display temperature-sensitive, seizure-like phenotypes (Jackson *et al*. 1984; Wang *et al*. 2004) indicating an involve-

ment of diverse types of molecules behind the phenotype.

To summarize, our work has led to the identification of a previously unknown locus for HWE at 9p24.3-p23, and has delimited a subgenomic region of about 10 Mb disease-underlying the disorder. With the evidence of at least three loci for HWE in India, we propose this clinical phenotype is genetically heterogeneous and requirement of further genetic studies to understand the clinical-molecular mechanisms involved.

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