

LETTERS/COMMENTARY

Association Analysis of *BRD2* (*RING3*) and Epilepsy in a Dutch Population

To the Editors:

The region between HLA-DQ and HLA-DP on 6p21 shows linkage to various syndromes within the idiopathic generalized epilepsy (IGE) spectrum, in particular to juvenile myoclonic epilepsy (JME) and visually sensitive syndromes (Greenberg et al., 1988; Durner et al., 1991; Weissbecker et al., 1991; Sander et al., 1997; Greenberg et al., 2000). Within this region, the gene *BRD2* (bromodomain containing 2) is a good positional candidate and three association studies using markers in *BRD2* have been published to date. The first is a study from the United States, which reported association with familial JME in patients of uncertain ethnic origin (Greenberg et al., 2000). The second study reported association between markers in the *BRD2* region and photoparoxysmal response (PPR) in German individuals, 59% of whom also had IGE. However, for SNPs that were typed in both studies, the associated alleles were alternative ones. A multicenter study subsequently typed an SNP (rs3918149) in the promoter that had been reported in the American study, in JME patients from five European populations and found significant association in Irish and British patients, but not in Germans (Cavalleri et al., 2007).

We have further investigated the SNP markers (rs188254, rs206781, and rs516535) in the 3'-end of the *BRD2* gene that showed the strongest association in the study with German individuals presenting with PPR. The SNPs were typed in a Dutch sample comprising 159 individuals with IGE, of whom 102 had JME and in 360 unrelated blood bank controls. For 33 patients, PPR or photo-sensitive epilepsy (PSE) was established, 71 were tested but were negative, while there was no information

about visual sensitivity for 55 patients. Taqman assays (Applied Biosystems, Foster City, CA, U.S.A.) were available for all three SNPs (assay ID C_1024346_20, C_1024338_10, C_1024346_20), and the analysis was carried out according to the manufacturer's specifications.

We found no significant difference between the allele frequencies in cases and controls for either of the markers (p-values >0.05; Table 1). For comparison, we have included the results from the previous two studies with those SNPs. In Table 2, the analysis is split into individuals with and without JME. Again, no significant differences were found.

Power to detect association at the level of $\alpha = 0.01$ in this study was around 55% if genotype relative risks were 2.0 in a dominant model. Had the risk been as high as 6, as reported by Pal et al. (2003) for their multilocus haplotype, the power would have been well above 90%. If a mutation in *BRD2* or its surrounding genes specifically causes PPR or epilepsy with PPR, this may have underpowered our study relative to samples consisting solely of JME patients—who have PPR more often—or of individuals selected for PPR. Our study, therefore, does not contradict the earlier findings, but neither can it support the hypothesis that *BRD2* or another gene in its neighborhood is involved in IGE or JME.

In summary, association between JME or PPR and the 3' end of *BRD2* has been found with alternative alleles in different studies, and some populations have shown association with the promoter region, which is in low linkage disequilibrium with the 3' end. Replication for both regions failed in some samples. Together, these results suggest the *BRD2* region is involved in JME, or possibly in visual

Table 1. Comparison of allele frequencies in cases and controls in two published studies and this study

SNP	Pal ^a (2003)		Lorenz ^b (2006)		This study		p-Value, this study
	Cases (20)	Controls (n.a.)	Cases (187)	Controls (666)	Cases (159)	Controls (360)	
rs516535_C	0.48	0.31	0.37	0.44	0.40	0.37	0.37
rs206781_T	0.70	0.65	0.56	0.63	0.60	0.58	0.68
rs188245_G	n.t. ^c	n.t.	0.53	0.46	0.48	0.52	0.33

Note: p-Values are for allele frequency differences between cases and controls in this study.

^aPal et al. (2003).

^bLorenz et al. (2006).

^cn.t., not tested.

Table 2. Comparison of genotype frequencies in different phenotypes (with percentages)

SNP	IGE/ not JME	JME	Total no. of cases (%)	Controls (%)	p (case- control)
rs516535					
CC	21	33	54 (37)	130 (41)	0.63
CT	28	39	67 (46)	133 (42)	
TT	10	16	26 (18)	51 (16)	
rs206781					
GG	13	15	28 (19)	66 (20)	0.88
GA	21	44	65 (43)	135 (42)	
AA	26	32	58 (38)	121 (38)	
rs188245					
AA	19	26	45 (31)	85 (26)	0.57
GA	24	37	61 (42)	145 (44)	
GG	15	25	40 (27)	96 (29)	

Note: p-Values are given for genotype frequency comparisons between all cases and controls.

sensitivity, but they are still inconclusive about which gene and what phenotype.

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Seizure Termination by Sensory Stimulation

To the Editors:

I read with interest the paper by Francisco Javier Carod-Artal et al. (2007). Epilepsy is generally perceived negatively as a lifelong incurable disorder and is frequently thought to be a punishment of evil deeds by many of the tribal people and rural populations in developing countries.

In our rural population, there are many misconceptions about the treatment of epilepsy. Many people will carry out traditional approaches to prevent the recurrence of seizures in epileptic patients and to terminate an active seizure. To prevent the recurrence of seizures, patients will sometimes be advised to wear metal rings or holy threads, or to eat the flesh of a black crow. However, the eating of bird or animal products to prevent epilepsy may lead to zoonotic diseases.

To terminate active seizures, most of our rural epileptic patients are offered the application of hot needles, or the giving of a key or hot or cool metal rod. Sometimes they are also exposed to the odor of onions, chilly powder, or the inhalation of tobacco dust to terminate the seizures. This type of sensory stimulation may terminate the seizure by activating cortico-cortical connections and causing hyperpolarization around the seizure focus. The mechanisms deserve further study to ascertain whether sensory feedback mechanisms are involved in the termination of an active seizure.

It is interesting to recall that the use of setons (threads drawn through the skin and tightened at times of seizures) were widely used in the 19th century to terminate seizures, and this practice was recommended by Hughlings Jackson. This may have involved the same mechanisms.

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Carod-Artal FJ, Vazquez Cabrera CB. (2007) An anthropological study about epilepsy in native tribes from Central and South America. *Epilepsia* 48(5):886–893.

NEXT MONTH IN *Epilepsia*

The December issue of *Epilepsia* will feature an Invited Commentary from Dr. Anne Berg on issues of research design and data analysis, particularly relevant to difficulties that arise in clinical/epidemiological research. Survey articles in this issue include a view of status epilepticus in a developing country, and an analysis of the cost of epilepsy in Europe. Other major themes in the December issue include: cognitive, intellectual, and psychiatric conditions associated with epilepsy; analysis of methods and avenues of antiepileptic therapies; and characterization of neural networks and EEG patterns associated with spike-wave activity and hypersarrhythmia. Finally, Gray Matters presents a discussion of drug resistance in epilepsy, with several groups of authors (Sisodiya and Goldstein, Löscher and Sills, Anderson and Shen) offering views on the current state of this important debate.

ONLINE EARLY

Berg, “Hypotheses, tests, methods, and innovation: The balancing act in research”

Biton et al., “Intravenous lacosamide as replacement for oral lacosamide in patients with partial-onset seizures”

Buechler et al., “Ictal scalp EEG recording during sleep and wakefulness: Diagnostic implications for seizure localization and lateralization”

Caraballo, et al., “Childhood occipital epilepsy of Gastaut: A study of 33 patients”

Chassoux et al., “Intralesional recordings and epileptogenic zone in focal polymicrogyria”

Clarke et al., “High risk of reading disability and speech sound disorder in rolandic epilepsy families: Case-control study”

Díaz-Otero, et al., “Autosomal dominant nocturnal frontal lobe epilepsy with a mutation in the *CHRNA2* gene”

Eriksson et al., “PROPELLER MRI visualizes detailed pathology of hippocampal sclerosis”

Friedman et al., “Cyclic electrographic seizures in critically ill patients”

Kossoff et al., “A prospective study of the modified Atkins diet for intractable epilepsy in adults”

Lossius et al., “Consequences of antiepileptic drug withdrawal: A randomized, double-blind study (Akershus Study)”

Lowenstein, “Pathways to discovery in epilepsy research: Rethinking the quest for cures”

Maton et al., “Surgery for medically intractable temporal lobe epilepsy during early life”

Nogueira de Almeida et al., “From lateral to mesial: The quest for a surgical cure for temporal lobe epilepsy”

Park et al., “Protective effect of topiramate on kainic acid-induced cell death in mice hippocampus”

Pastor et al., “Morbidity associated with the use of foramen ovale electrodes”

Ragheb and Duchowny, “Surgery for medically intractable temporal lobe epilepsy during early life”

Rakhade and Loeb, “Focal reduction of neuronal glutamate transporters in human neocortical epilepsy”

Schuele et al., “Ictal asystole: A benign condition?”

Toro et al., “The NR1 N-methyl-D-aspartate subunit and brain-derived neurotrophic factor in temporal lobe epilepsy hippocampus: A comparison of patients with and without coexisting psychiatric symptoms”

Zangaladze et al. “The effectiveness of low-frequency stimulation for mapping cortical function”

ANNOUNCEMENTS

61st American Epilepsy Society Annual Meeting

The city of Brotherly Love, Philadelphia, Pennsylvania, USA will host the 2007 Annual Meeting of the American Epilepsy Society, November 30–December 4, 2007. This 5-day congress features symposia on hot topics such as “Generic Antiepileptic Drug Substitution” and “Post Traumatic Epilepsy” in addition to the Investigators’ Workshops, Special Interest Groups, Plenary Sessions and Evening Symposia. Details on the meeting, including procedures for online registration and housing reservations, are available on the AES web-site: <http://www.aesnet.org>.

International Symposium on Febrile Seizures and Related Conditions

The Infantile Seizure Society (ISS—Chairperson, Yukio Fukuyama) will host the International Symposium on Febrile Seizures and Related Conditions (ISFS President, Yoshihiro Takeuchi) in Otsu, Japan on April

10–11, 2008. Febrile seizures are the most common types of seizures experienced by infants and young children. However, many questions in both the basic and the clinical arenas still remain unresolved. The ISFS aims to present a comprehensive update of the topic, and will include discussions on such issues as genetics, epidemiology, pathophysiology, imaging, treatment, education, and subsequent related conditions (including epilepsy and mesial temporal sclerosis).

This Symposium represents the 11th Annual Meeting of the ISS. For additional information see the symposium website at: <http://www.iss-jpn.info/> or send an e-mail to Tomoyuki Takano, secretary of the ISFS, at: iss2008@belle.shiga-med.ac.jp

7th Asian & Oceanian Epilepsy Congress

The 7th Asian & Oceanian Epilepsy Congress (AOEC) will take place in beautiful Xiamen on the southeast coast of China, May 15–18, 2008. The Scientific Program will include main sessions, and post main sessions mixed with interesting parallel sessions and platform sessions. The abstract submission deadline is January 15, 2008. The early registration deadline is February 15, 2008. For more information go to: <http://www.epilepsyxiamen2008.org/>

CALENDAR OF MEETINGS

2007

November 2007

- **International Symposium: Fifty Years of Landau–Kleffner Syndrome: A Tribute to William Landau & Frank Kleffner**

2–4 November

Alden-Biesen, Belgium

<http://www.lks-symposium.eu/>

2008

May 2008

- **7th Asian & Oceanian Epilepsy Congress**

15–18 May

Xiamen, China

<http://www.epilepsyxiamen2008.org>

August 2008

- **Venice Epilepsy Summer School, 7th International Course: Bridging Basic with Clinical Epileptology-3**

August 2008

Venice, Italy

email: epilepsysummercourse@univiu.org

September 2008

- **8th European Congress on Epilepsy**

21–25 September

Berlin, Germany

<http://www.epilepsyberlin2008.org>

November 2008

- **5th Congreso Latinoamericano de Epilepsia (ILAE & IBE)**

5–8 November

Montevideo, Uruguay

<http://www.epilepsymontevideo2008.org>