SUMMARY

Purpose: Several recent reports of genomic microdeletions in epilepsy will generate further research; discovery of more microdeletions and other important classes of variants may follow. Detection of such genetic abnormalities in patients being evaluated for surgical treatment might raise concern that a genetic defect, possibly widely expressed in the brain, will affect surgical outcome.

Methods: A reevaluation was undertaken of clinical presurgical data, histopathology of surgical specimen, and postsurgical outcome in patients with mesial temporal lobe epilepsy (MTLE) who have had resective epilepsy surgery, and who have been found to have particular genomic microdeletions.

Key Findings: Three thousand eight hundred twelve patients with epilepsy were genotyped and had a genome-wide screen to identify copy number variation. Ten patients with MTLE, who had resective epilepsy surgery, were found to have 16p13.11 microdeletions or other microdeletions >1 Mb. On histopathology, eight had classical hippocampal sclerosis (HS), one had nonspecific findings, and one had a hamartoma. Median postsurgical follow-up time was 48 months (range 10–156 months). All patients with HS were seizure-free after surgery, International League Against Epilepsy (ILAE) outcome class 1, at last follow-up; the patient with nonspecific pathology had recurrence of infrequent seizures after 7 years of seizure freedom. The patient with a hamartoma never became seizure-free.

Significance: Large microdeletions can be found in ‘‘typical’’ MTLE. In this small series, patients with MTLE who meet criteria for resective surgery and harbor large microdeletions, at least those we have detected, can have a good postsurgical outcome. Our findings add to the spectrum of causal heterogeneity of MTLE + HS.

KEY WORDS: Epilepsy surgery, Hippocampal sclerosis, Temporal lobectomy, Deletions.
represent widespread brain involvement, similar to cognitive impairment or secondary generalized tonic–clonic seizures, both of which reduce chances of good outcome across various domains after epilepsy surgery (Malmgren et al., 2008; Spencer & Huh, 2008). On the other hand, such microdeletions might not affect outcome, for example because of spatial variability in gene expression (Hardy et al., 2009). We evaluated systematically the effect of large microdeletions on outcome after surgery in patients with MTLE.

**Methods**

This work was approved by the relevant local research ethics committees. All patients provided written informed consent.

Microdeletions were identified as described previously (Heinzen et al., 2010). Only microdeletions >1 Mb, or 16p13.11 microdeletions, were considered (Heinzen et al., 2010). We reevaluated clinical history and presurgical investigations [magnetic resonance imaging (MRI) brain scan, video–electroencephalography (EEG) telemetry, neuropsychometry, neuropsychiatric assessment]. Histopathology of the surgical specimen was reviewed. Post-surgical outcome was evaluated in terms of seizure control at 1 year and at last follow-up, using the International League Against Epilepsy (ILAE) outcome classification (Wieser et al., 2001), antiepileptic drug changes, psychiatric outcome, neuropsychometry, and employment outcome.

**Results**

Three thousand eight hundred twelve patients with epilepsy (>90% with partial epilepsies) were genotyped and had a genome-wide screen to identify copy number variation. Ten patients with MTLE who had undergone therapeutic resection had large microdeletions. Follow-up duration after surgery ranged from 10–156 months. Three patients had 16p13.11 microdeletion and two had 15q11.2 microdeletion; the full range of microdeletions is listed in Table 1.

Demographic and clinical data are summarized in (Table S1), including details of the type of surgery and outcome of surgery across several domains, including seizure control. The histopathologic results from analysis of the surgical specimen are listed in Table 2.

Eight patients had histologically proven classical hippocampal sclerosis (HS) (Table 2). All were rendered seizure-free after surgery. All displayed clinical features “typical” of MTLE + HS (Wieser, 2004) (Table S1). In all patients except one, antiepileptic drugs (AEDs) were reduced in number and/or daily dose during long-term follow-up. Two patients were off AEDs; they had remained seizure-free at last follow-up.

Another patient, with MRI-negative temporal lobe epilepsy, had a right neocorticectomy and amygdaloectomy, with nonspecific findings at histopathology, and after 7 years of seizure freedom, began again to have infrequent partial seizures. One patient with a hamartoma had a right anterior temporal lobectomy, but was never rendered seizure-free. There were no unexpected findings in other domains during postsurgical follow-up.

**Discussion**

In patients with drug-resistant MTLE + HS, surgery is more effective in stopping disabling seizures than medical treatment alone (Wiebe et al., 2001). Recent studies also suggest that such surgery can benefit longevity (Choi et al., 2008) and quality of life (Zupanc et al., 2010). Around one-third of patients who undergo surgery fail to become seizure-free, the causes for which are uncertain; the proportion not seizure-free increases at longer-term follow-up.

| Case ID | Cytoband | Breakpoints | Size (Mb) | Gene list |
|---------|----------|-------------|-----------|-----------|
| 1 16p13.11 | chr16:15387380–16225138 | 0.8 | MPV17L, C16orf45, NDE1, MYH11, C16orf63, ABCCI, ABCB6 |
| 2 16p13.11 | chr16:15387380–16225138 | 0.8 | MPV17L, C16orf45, NDE1, MYH11, C16orf63, ABCCI, ABCB6 |
| 3 7q31.32–31.33 | chr7:123252578–126117199 | 2.9 | HYAL4, SPAM1, LOCL36157, GPR37, POT1, GRM8 |
| 4 17p12 | chr17:14040467–15411904 | 1.4 | COX10, CDRT15, H35ST3B1, PMP22, TEKT3, CDRT4, FAM18B2 |
| 5 4q32.3 | chr4:167446375–168643447 | 1.2 | SPOCK3 |
| 6 17q12 | chr17:31922987–33333394 | 1.4 | ZNH1T3, MYO19, PIGW, GGNB2, DHR51, L1RM1, LHX1, AATF, ACACA, C17orf78, TAD21, DUSP14, AGIP1, DDX32, HNF1B, LOC284100 |
| 7 15q11.2 | chr15:18285782–20868229 | 1.3 | OR4N4, NIPA2, NIPA1, TUBGCP5, CYFIP1, HERC2P2, A26B1 (POTEB), OR4M2, AC131280.9, AC126603.9, AC116135.7, AC026495.13, AC025884.28, AC138701.3, AC127381.14, AC126335.16, AC091565.10, AC138649.2 |
| 8 15q11.2 | chr15:18822307–19852603 | 1.0 | AC025884.28, AC026495.13, OR4N4, OR4M2, AC131280.9, AC134980.3, AC126335.16, A26B1 |
| 9 4q32.3 | chr4:189052964–190737252 | 1.97 | AC093909.2, AC020698.4, TRIML2, TRIML1, ZFP42 |
| 10 16p13.11 | chr16:15387380–16198600 | 0.8 | MPV17L, C16orf45, NDE1, MYH11, C16orf63, ABCCI, ABCB6 |
and noted that many known epilepsy genes, for example, changes in gene expression with 16p13.11 microdeletions, with disease (Scheffer & Berkovic, 2010), and we showed findings, large microdeletions are likely to be associated of epilepsies. Although some microdeletions may be chance potential genetic cause of, or predisposition to, a wide range Kasperaviciute et al., 2010).

Stögmann et al., 2002; Cavalleri et al., 2005, 2007; leptosurgery, has been confirmed (Kanemoto et al., 2000; 2009). No genetic cause of familial MTLE is known. In MTLE + HS (Kobayashi et al., 2003a; Gambardella et al., 2010). Some argue that familial MTLE with HS/hippocam-

Genetic factors might be postulated to contribute to outcome, and indeed to causation of MTLE + HS. Familial MTLE exists (Berkovic et al., 1994, 1996; Crompton et al., 2010). Some argue that familial MTLE with HS/hippocampal atrophy is clinically indistinguishable from sporadic MTLE + HS (Kobayashi et al., 2003a; Gambardella et al., 2009). No genetic cause of familial MTLE is known. In addition, no genetic determinant for susceptibility to sporadic MTLE + HS, or for predicting outcome after epilepsy surgery, has been confirmed (Kanemoto et al., 2000; Stögmann et al., 2002; Cavalleri et al., 2005, 2007; Kasperaviciute et al., 2010).

Microdeletions are becoming recognized as an important potential genetic cause of, or predisposition to, a wide range of epilepsies. Although some microdeletions may be chance findings, large microdeletions are likely to be associated with disease (Scheffer & Berkovic, 2010), and we showed changes in gene expression with 16p13.11 microdeletions, and noted that many known epilepsy genes, for example, KCNA1, GABRA1, and GABRG2, can be involved in microdeletions (Heinzen et al., 2010). It is important to note that many of these microdeletions seem to act as risk factors rather than as the sole underlying cause, and that some microdeletions are found in people without epilepsy or a family history of epilepsy, although at much reduced frequency (Sisodiya & Mefford, 2011). Although more work is required to characterize microdeletions and their pathogenic mechanisms, significant microdeletions are likely to be found in many other patients, including those being considered for epilepsy surgery. Because these microdeletions might affect outcome after surgical treatment, it is important to systematically evaluate their influence.

The seizure-free rate in our patients with putatively path-
ogenic microdeletions seems as good as reported for cohorts in the literature (McIntosh et al., 2001; Spencer & Huh, 2008; Dunlea et al., 2010). Although this observation must be tempered by the small size of our microdeletion cohort and requires further confirmation, we show that having a large microdeletion does not preclude seizure-free outcome after surgery for MTLE. Although our findings may relate to specific microdeletions, our seizure-free patients had seven different microdeletions, and had a good postsurgical outcome in other domains as well, not just seizure control (Table S1). The psychiatric outcome varied, with presurgical psychiatric comorbidity common in the cases with postsurgical psychiatric issues, as reported previously in the literature (Kanner et al., 2009).

There are other examples in the literature of epilepsies with a genetic basis and a good outcome after resective
surgery for drug-resistant seizures. In families with SCN1B-positive genetic epilepsy with febrile seizures plus (GEFS+), an excellent outcome has been reported after anterior temporal lobectomy for affected individuals with drug-resistant MTLE + HS (Scheffer et al., 2007). A small series of patients with tuberous sclerosis complex, with confirmed mutations in the TSC1 (n = 2) and TSC2 (n = 2) genes, had discrete epileptogenic brain lesions that were resected, and were seizure-free on AEDs at last follow-up after surgery (Hirfangolu & Gupta, 2010). Posturgical seizure outcome in patients with familial MTLE with HS/hippocampal atrophy, for which no known genetic cause is actually yet known, does not differ from that in sporadic MTLE with HS/hippocampal atrophy (Kobayashi et al., 2003b).

Our findings suggest that large microdeletions do not necessarily preclude a good prognosis following epilepsy surgery, if surgery is a reasonable option based on concordance of other data during presurgical evaluation. Further studies will be important to firmly establish the mechanisms of MTLE associated with large microdeletions. As more putatively causal genetic variants of all classes are uncovered, it will also become important to address their impact on clinical management.

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DISCLOSURES

Dr. Cavalleri holds a corporate appointment with GeneChronicle. Dr. Dorn has received honoraria for talks and organizing symposia as well as funding for travel from UCB, Janssen-Cilag, Desitin Arzneimittel, and Eisai Pharma. Dr. Depondt has received funding for travel from UCB. Dr. Krämer has received honoraria for serving on scientific advisory boards, funding for travel, giving talks, or support for scientific research from Desitin Arzneimittel, Eisai Pharma, GlaxoSmithKline, Janssen-Cilag, Pfizer, and UCB. He serves as editor of the journals “Aktuelle Neurologie” and “Epileptologie” and is member of the editorial advisory board of “Epileptology” and “Zeitschrift für Epileptologie.” Dr. Delanty has received honoraria for serving on national and international advisory boards of UCB Pharma, Eisai Pharmaceuticals, Janssen-Cilag, and GSK Ltd; and has received honoraria for speaking at symposia sponsored by UCB Pharma, Eisai Pharmaceuticals, and GSK Ltd. Dr. Delanty serves on the Independent Data Monitoring Committee of a clinical trial sponsored by Lundbeck Inc. Dr. Delanty is the principal investigator of the Irish component of the UK and Irish Epilepsy and Pregnancy Register, which has received funding from UCB Pharma, Eisai Pharmaceuticals, Janssen-Cilag, GSK Ltd, Pfizer Inc, and Sanofi Aventis. The Epilepsy Research Programme at Beaumont Hospital has received financial support from the Higher Education Authority of Ireland, the Irish Health Research Board, Science Foundation Ireland, and Brainwave, The Irish Epilepsy Association. Dr. Sisodiya has received research support, honoraria, or consultancy fees from UCB, Lundbeck, and GSK. The remaining authors have no conflicts of interest. 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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