CHD2 variants are a risk factor for photosensitivity in epilepsy

Elizabeth C. Galizia,1,2,* Candace T. Myers,3,* Costin Leu,1,2,* Carolien G. F. de Kovel,4 Tatiana Afrikanova,5 Maria Lorenza Cordero-Maldonado,5 Teresa G. Martins,5 Maxime Jacmin,5 Suzanne Drury,6 V. Krishna Chinthapalli,1,2 Hiltrud Muhle,7 Manuela Pendziwiat,7 Thomas Sander,8 Ann-Kathrin Ruppert,8 Rikke S. Møller,9,10 Holger Thiele,8 Roland Krause,5 Julian Schubert,11 Anna-Elena Lehesjoki,12,13 Peter Nürnberg,8 Holger Lerche11 for the EuroEPINOMICS CoGIE Consortium, # Aarno Palotie,14,15,16 Antonietta Coppola,1,2,17 Salvatore Striano,17 Luigi Del Gaudio,17 Christopher Boustred,6 Amy L. Schneider,18 Nicholas Lench,6 Bosanka Jocic-Jakubi,19,20 Athanasios Covannis,21 Giuseppe Capovilla,22 Pierangelo Veggiotti,23,24 Marta Piccioli,25 Pasquale Parisi,26 Laura Cantonetti,27 Lynette G. Sadleir,28 Saul A. Mullen,29 Samuel F. Berkovic,18 Ulrich Stephani,7 Ingo Helbig,7 Alexander D. Crawford,5 Camila V. Esguerra,30,31 Dorothee G. A. Kasteleijn-Nolst Trenité,4 Bobby P. C. Koeleman,4,$ Heather C. Mefford,3,5 Ingrid E. Scheffer,18,29,$ and Sanjay M. Sisodiya1,2,$

* These authors contributed equally to this work.
# For details of the EuroEPINOMICS CoGIE Consortium see Appendix 1.

Photosensitivity is a heritable abnormal cortical response to flickering light, manifesting as particular electroencephalographic changes, with or without seizures. Photosensitivity is prominent in a very rare epileptic encephalopathy due to de novo CHD2 mutations, but is also seen in epileptic encephalopathies due to other gene mutations. We determined whether CHD2 variation underlies photosensitivity in common epilepsies, specific photosensitive epilepsies and individuals with photosensitivity without seizures. We studied 580 individuals with epilepsy and either photosensitive seizures or abnormal photoparoxysmal response on electroencephalography, or both, and 55 individuals with photoparoxysmal response but no seizures. We compared CHD2 sequence data to publicly available data from 34 427 individuals, not enriched for epilepsy. We investigated the role of unique variants seen only once in the entire data set. We sought CHD2 variants in 238 exomes from familial genetic generalized epilepsies, and in other public exome data sets. We identified 11 unique variants in the 580 individuals with photosensitive epilepsies and 128 unique variants in the 34 427 controls: unique CHD2 variation is over-represented in cases overall (P = 2.17 x 10^-5). Among epilepsy syndromes, there was over-representation of unique CHD2 variants (3/36 cases) in the archetypal photosensitive epilepsy syndrome, eyelid myoclonia with absences (P = 3.50 x 10^-4). CHD2 variation was not over-represented in photoparoxysmal response without seizures. Zebrafish larvae with chd2 knockdown were tested for photosensitivity. Chd2 knockdown markedly enhanced mild innate zebrafish larval photosensitivity. CHD2 mutation is the first identified cause of the archetypal generalized photosensitive epilepsy syndrome, eyelid myoclonia with absences. Unique CHD2 variants are also associated with photosensitivity in common epilepsies. CHD2 does not encode an ion channel, opening new avenues for research into human cortical excitability.

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1 NIHR Biomedical Research Centre Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK
2 Epilepsy Society, Bucks, UK
3 Department of Paediatrics, University of Washington, USA
4 Department of Medical Genetics Research, University Medical Centre Utrecht, The Netherlands
5 Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg
6 North East Thames Regional Genetics Laboratories, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
7 Department of Neuropaediatrics, University Medical Centre Schleswig-Holstein and Christian-Albrechts-University of Kiel, Kiel, Germany
8 Cologne Centre for Genomics, University of Cologne, Cologne, Germany
9 Danish Epilepsy Centre, Dianalund, Denmark
10 Institute for Regional Health Services, University of Southern Denmark, Odense, Denmark
11 Department of Neurology and Epileptology, Hertie Institut for Clinical Brain Research, Tübingen, Germany
12 Folkhälso Institute of Genetics and Neuroscience Centre, University of Helsinki, Helsinki, Finland
13 Research Programs Unit, Molecular Neurology, University of Helsinki, Helsinki, Finland
14 Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, UK
15 Institute for Molecular Medicine Finland, University of Helsinki, Helsinki, Finland
16 Program in Medical and Population Genetics and Genetic Analysis Platform, The Broad Institute of MIT and Harvard, Cambridge, USA
17 Epilepsy Centre, Neurology Department, Federico II University of Naples, Naples, Italy
18 Department of Medicine, University of Melbourne, Austin Health, Melbourne, Australia
19 Department of Child Neurology, Paediatric Clinic, Clinical Centre Nis, Serbia
20 Department of Paediatric Neurology, Paediatric Clinic, Al Sabah Hospital, Kuwait
21 Neurology Department, The Children’s Hospital Agia Sophia, Athens, Greece
22 Epilepsy Centre ‘C. Poma Hospital’, Mantova, Italy
23 Department of Child Neurology and Psychiatry C. Mondino National Neurological Institute, Via Mondino, 2, 27100, Pavia, Italy
24 Brain and Behaviour Department, University of Pavia, Pavia, Italy
25 Neurophysiopathology Unit, San Filippo Neri Hospital, Rome, Italy
26 Child Neurology, NESMOS Department, Faculty of Medicine and Psychology, Sapienza University, Rome, Italy
27 Neurorehabilitation Unit, Department of Neuroscience and Neurorehabilitation, IRCCS, Bambino Gesu’ Children’s Hospital, Rome, Italy
28 Department of Paediatrics and Child Health, School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand
29 Florey Institute of Neurosciences and Mental Health, and Department of Paediatrics, University of Melbourne, Royal Children’s Hospital, Melbourne, Australia
30 Chemical Neuroscience Group, Biotechnology Centre of Oslo, University of Oslo, Oslo, Norway
31 Laboratory for Molecular Biodiscovery, University of Leuven, Leuven, Belgium

Correspondence to: Sanjay M Sisodiya, Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK
E-mail: s.sisodiya@ucl.ac.uk

Correspondence may also be addressed to:
Ingrid E. Scheffer, Epilepsy Research Centre, Austin Health, 245 Burgundy St, Heidelberg, Victoria 3081, Australia
E-mail: scheffer@unimelb.edu.au

Heather C. Mefford, Department of Pediatrics, Division of Genetic Medicine, 1959 NE Pacific St., Box 356320, Seattle, WA 98195, USA
E-mail: hmefford@uw.edu
Photosensitivity occurs in some epileptic encephalopathies, such as Dravet syndrome due to mutation in SCN1A and encephalopathy associated with mutation in CHD2 (Carvill et al., 2013). Published data do not allow determination of whether the photosensitivity in these conditions is due to the underlying gene mutation or to the epileptic encephalopathy per se. CHD2 encodes chromodomain helicase DNA-binding protein 2, involved in transcriptional regulation. Additional attention was drawn to CHD2 as a candidate photosensitive epilepsy gene as the only shared gene within several reported overlapping copy number variants of the chromosome 15q26.1 region associated with complex phenotypes including epilepsy with photosensitivity. Eight patients with de novo deletions of 15q26 encompassing part or all of CHD2 have been reported (Veredic et al., 2009; Dhamija et al., 2011; Capelli et al., 2012; Lund et al., 2013; Mullen et al., 2013; Chénier et al., 2014). We and others subsequently showed 6/500 epileptic encephalopathy cases had de novo CHD2 mutations (Carvill et al., 2013; Epileptic Encephalopathy 4K Consortium, 2013; Sulis et al., 2013; Lund et al., 2014), and recently showed that clinical photosensitivity was prominent in the rare CHD2-associated myoclonic encephalopathy (Thomas et al., 2015).

These findings led us to hypothesize that CHD2 disruption would be associated with common forms of photosensitive epilepsy or photosensitivity manifesting as a photoparoxysmal response alone.

**Materials and methods**

Written informed consent was obtained from patients or parents/guardians for minors or those with intellectual disability. The study was approved by relevant institutional ethics committees.

We defined photosensitive epilepsy as the presence of a photoparoxysmal response (Kastelein-Nolst Trenité et al., 2012) with a history of epilepsy, or seizures reproducibly induced by flickering light. The photoparoxysmal response per se was not an essential inclusion requirement in every patient with epilepsy because age, state (e.g. sleep deprivation) and antiepileptic medication affect its detectability. To test the effect of CHD2 variation beyond the epileptic encephalopathies alone, we included a broad range of epilepsy types. Recruitment was from nine countries (see Supplementary Material).
material for details) (Tauer et al., 2005; Lu et al., 2008; Taylor et al., 2013). The cohort included 36 patients with EMA: all had photoparoxysmal response. We sequenced CHD2 in 580 people with photosensitive epilepsy and 55 people with photoparoxysmal response but no history of seizures. All patients were of European ancestry. The phenotypic distribution is given in Table 1.

We evaluated data from two additional exome-sequenced cohorts of GGE patients, to determine the role of CHD2 variation in GGE per se, independent of photoparoxysmal response. Not all patients in these cohorts had been formally assessed for photoparoxysmal response. These two groups were the Complex Genetics of Idiopathic Epilepsies Consortium (CoGIE) cohort of 238 probands with familial GGE (Supplementary material), and a published cohort of 118 patients with GGE (Heinzen et al., 2012).

Targeted sequencing of CHD2 was undertaken either using Illumina TruSeq Custom Amplicon™ (TSCA) or molecular inversion probes (see Supplementary material for details). Whole exome sequencing (Supplementary material) was performed on five EMA samples. Coverage data for all experiments are provided in the Supplementary material. Only variants confirmed by a second method (Sanger sequencing or a second independent molecular inversion probe capture, see Supplementary material) were used in analyses.

The Exome Aggregation Consortium (ExAC) formed a large control population of disease and population genetic studies (ExAC, Cambridge, USA; URL: http://exac.broadinstitute.org accessed October 2014; non-Finnish European samples only used), giving the best available population frequency of CHD2 variants of interest. Detailed phenotypic data are not available for these individuals; some might, if tested, have or have had photoparoxysmal response or history of photosensitive seizures. These unselected cases are unlikely to harbour more than the best estimates of photoparoxysmal response prevalence in the general population (1.4%) (Kasteleijn-Nolst Trenite et al., 2003).

We focused on unique variants, in our cohort and in ExAC: this is a well-established approach (Carvill et al., 2013; Cnossen et al., 2014; Wain et al., 2014). We hypothesized an over-representation of unique variants in our cohort compared with the phenotypically-unselected ExAC cohort. We defined unique variants as those that occurred in one individual only, in cases and controls (from ExAC) considered together, that were non-synonymous, splice-site or frameshift. We used several methods for prediction of the functional consequences of unique variants in cases (Supplementary material). We defined ‘rare’ variants as those with a minor allele frequency <1% in the non-Finnish European ExAC samples.

We undertook functional studies. To test functional consequences of Chd2 loss in zebrafish, we used the chd2 E122 morpholino reported previously (Suls et al., 2013). Briefly, morpholino (12 ng) was microinjected into 1- to 2-cell-stage embryos of the AB (wild-type) strain. Embryos were raised in a dark incubator. At 1 day post-fertilization (dpf), embryos were prepared using the least possible amount of light. In parallel, control non-injected embryos from the same clutch of eggs were processed in the same manner. At 4 dpf, optic tectal field recordings were performed (Suls et al., 2013) (Supplementary material). The first 10 s of recording were performed in minimal light in order to place the needle. Immediately following these first 10 s, recordings were performed in the dark for five minutes. At the end of this 5-min period, a very bright light was switched on (‘light ON’ state; six times the standard brightness level used for needle placement), and recording continued for 5 min. A paroxysm of high-frequency activity (200–500 Hz) with amplitude >3 times background level, either spontaneous or evoked by light, was defined as a polyspiking episode.

Statistics

We performed a two-tailed Fisher’s exact test to determine whether the burden of unique variants in our case cohorts was greater than expected compared to ExAC controls. We examined the frequency of all rare variants in the entire cohort, and the frequency of unique variants only separately in patients with EMA, patients with GGE excluding EMA, and patients with focal epilepsies. The threshold for significance was set at P < 0.01, applying Bonferroni correction for these five comparisons. For the single separate comparison of cases with photoparoxysmal response without epilepsy and ExAC, significance was set at P < 0.05. For zebrafish data, comparison of the parameters of spiking activity (dark versus light condition) for each treatment group was performed using the Mann-Whitney test.

Results

We identified 22 rare variants (Supplementary Table 1) in the cohort of patients with photosensitive epilepsy: 11 were unique (Table 2). There was a significant difference (P = 2.17 × 10−5) in unique variant frequency between cases (11/580 cases; 11/1160 alleles; 0.95%) and controls (128/68 854 alleles; 0.19%). The unique variants in the cases were all well covered in ExAC controls (Supplementary material). The 11 unique variants in cases were also absent from additional data sets: Exome Variant Server (http://evs.gs.washington.edu/EVS/), 1000 Genomes data set (http://www.1000genomes.org/), and dbSNP
There was no difference in the overall burden of rare CHD2 variants in cases compared to controls (22/1160 alleles (1.90%) versus 1236/68854 alleles (1.80%) respectively; \( P = 0.74 \)). We provide data on the frequency of variants in CHD2 in cases and controls according to various thresholds in the Supplementary Table 2. Figure 1 shows all previously-reported variants and all unique variants identified in our cases.

We investigated the predicted deleteriousness of the 11 unique variants in the cases (Table 2). Eight of 11 unique variants (73%) had scaled CADD scores >10, placing them in the top 10% most deleterious single nucleotide variants; as a group, the 11 variants had a mean scaled CADD score of 32.6, ranking higher than 99.95% of all possible human single nucleotide variants (Kircher et al., 2014).

Next, we analysed variation by epilepsy type. The archetypal photosensitive GGE syndrome EMA had the highest frequency of unique variants, found in 3/36 patients, more than expected compared to ExAC controls (3/72 alleles versus 128/68854 alleles) (\( P = 3.50 \times 10^{-4} \)). As a post hoc comparison, the frequency of unique variants (4.2%) in the small EMA group is considerably greater than in our overall cohort excluding EMA (0.74%) (\( P = 0.026 \)). Notably, two of three EMA variants were frameshift, compared to 9/128 unique variants in ExAC. One EMA variant was shown to have arisen de novo, strengthening its role in causation of the phenotype.

For all GGE excluding EMA, we found no significant difference compared to ExAC (4/888 alleles versus 128/68854 alleles, \( P = 0.089 \)). We also did not find significant over-representation in focal epilepsies compared with ExAC (2/118 alleles versus 128/68854 alleles; \( P = 0.021 \)). One case was included in both GGE and focal epilepsy cohorts, as the phenotype evolved from early-onset absence epilepsy to idiopathic photosensitive occipital epilepsy (Patient 11, Table 2). One of 55 (1.82%) individuals with photoparoxysmal response but no seizures had a unique CHD2 variant (Table 2 and Fig. 1): this did not represent over-representation compared to ExAC (1/110 alleles versus 128/68854 alleles; \( P = 0.186 \)). This case has not developed epilepsy by the age of 18 years. We provide 99% confidence intervals (CI) (accounting for multiple comparisons) for all these comparisons in Table 3.
without photoparoxysmal response. Of 238 CoGIE GGE probands (Supplementary material), none had unique CHD2 variants (not seen in ExAC or our cases). There were no unique mutations in CHD2 in a previously-published cohort of 118 patients with GGE (Heinzen et al., 2012).

To test functional consequences of Chd2 loss in zebrafish, we used the chd2 E212 morpholino reported previously (Suls et al., 2013). As described, chd2 morpholino-injected larvae displayed body curvature, excessive body pigmentation, and developmental delay (Suls et al., 2013). This phenotype was observed after 50% knockdown of chd2. All non-treated larvae appeared normal. Recordings were obtained from 15 morpholino-injected larvae and 10 sibling controls. In comparison to 7 dpf larvae (Afrikanova et al., 2013), spikes from 4 dpf larvae were shorter in duration and displayed a higher frequency of oscillations in polyspike complexes. Due to these differences, spontaneous spiking in controls was not excluded, but also quantified. We analysed duration of discharges, number of discharges under light conditions, cumulative duration of spiking activity, and cumulative discharge frequency distribution. Representative recordings are shown in Fig. 2.

In line with the previous findings (Suls et al., 2013), the morpholino-injected larvae showed spontaneous abnormal burst discharges. There was a preferential occurrence during the light ON state (17 discharges in the dark versus 59 in the light). In the morpholino-injected group, 14/15 larvae had discharges during the light ON state; 7/15 larvae had spiking only during the 5-min light ON state, and 10/15 showed spiking activity within the first 3–5 s after the light was switched on. However, the overall distribution of event duration is different from that of morpholino-injected larvae (Fig. 3D): the controls’ curve lies to the left of the morpholino-injected curve, indicating that the proportion of longer discharges is higher in the morpholino-injected group.

| Table 3 | Odds ratio for association with unique variants in CHD2 by phenotype, with 99% CI |
|---------|--------------------------------------------------------|
|          | P-value (Fisher’s exact; 2-tailed) | Odds ratio | Lower bound of 99% CI | Upper bound of 99% CI |
| Whole photosensitive epilepsy cohort | 2.17 × 10⁻⁵ | 5.18 | 2.29 | 11.74 |
| EMA alone | 3.30 × 10⁻⁴ | 24.36 | 5.06 | 117.38 |
| GGE excluding EMA | 0.089 | 2.44 | 0.65 | 9.08 |
| Focal epilepsies | 0.021 | 9.40 | 1.45 | 61.01 |
| Cases with PPR only | 0.186 | 4.96 | 0.36 | 67.74 |

The associations with photosensitive epilepsy overall and with EMA alone are significant, as documented in the text. PPR = photoparoxysmal response.

Figure 1 Schematic of CHD2 illustrating its functional (chromo, DEXDc, DNA-binding and ATP helicase) domains, the location of previously-reported variants and the unique variants in both cases and controls identified in this study.
Discussion

We show an enrichment of unique variants in CHD2 with photosensitivity in the common epilepsies overall, identifying CHD2 as a photosensitive epilepsy gene. We also examined the distribution of unique variants by syndrome. CHD2 is also the first gene to be discovered for EMA, the archetypal photosensitive epilepsy syndrome. In CHD2 encephalopathy, though published phenotypes can be difficult to interpret, the seizure type of absence seizures with eyelid myoclonia, rather than the epilepsy syndrome, is seen in as many as 8/23 (35%) patients with de novo CHD2 mutation or deletion (Veredice et al., 2009; Dhamija et al., 2011; Capelli et al., 2012; Carvill et al., 2013; Chénier et al., 2014; Lund et al., 2014). Together, these results suggest that CHD2 is an important contributor to both the absence seizures with eyelid myoclonia seizure type and EMA epilepsy syndrome. For other epilepsy syndromes, CHD2 variation over-representation in the photosensitive GGE or the mixed cohort of photosensitive focal epilepsies failed to meet the corrected threshold for significance. A single unique CHD2 variant was found in one patient with photoparoxysmal response without seizures. In view of the comparatively small sizes of these syndrome cohorts, we can only confidently exclude effects with odds ratios greater than the upper limit for the 99% confidence intervals given in Table 3. Further studies in larger cohorts of these phenotypes would seem warranted.

Previous studies of photoparoxysmal response support a model of significant genetic heterogeneity and an overall complex genetic architecture (Sadleir et al., 2012; Verrotti et al., 1997; Schuster et al., 2002; Kulkarni et al., 2008). Chd2 knockdown zebrafish have multiple developmental abnormalities, abnormal movements and epileptiform discharges (Suls et al., 2013). Disruption of Chd2 in mice causes embryonic death in some heterozygote pups and a complex phenotype including growth retardation and lordokyphosis (Marfella et al., 2006; Kulkarni et al., 2008): epilepsy has not yet been described. Interestingly, the reported human mutations do not cluster to accessory domains of the protein and no obvious pattern has emerged. Recent data demonstrated that the N-terminal region of CHD2 plays an inhibitory role, reducing DNA affinity and ATPase activity which may confer specificity, while the C-terminus enhances DNA binding and stimulates ATPase activity.

Figure 2  Representative tectal field recordings of 4-dpf zebrafish larvae. Background fragment of non-treated wild-type control in the dark (A); reaction of a non-injected fish to light ON - movement artefacts (wavy background) and a very short spike were observed (B); response to light ON of the morpholino-injected larvae: significantly more spiking activity is seen (C). The scale is the same for all three fragments.
Additional studies investigating protein interacting partners and post-translational modifications of CHD2 will be necessary to understand how abnormal CHD2 leads to photosensitive epilepsy.

Our zebrafish data show that partial (50%) loss of chd2 function causes photosensitivity. Although Suls et al. (2013) showed chd2 knockdown could cause seizures, photosensitivity was not studied. Although normal zebrafish show complex sensitivity to light (Moore and Whitmore, 2014), and untreated larvae show minor sensitivity to sudden exposure to light, morpholino-injected larvae show significantly more spiking activity on sudden light exposure. Photosensitivity on constant, rather than only flickering, light exposure has been described in humans (Oguni et al., 2001). The functional consequences of each of the human mutations we detected is not known, but some at least very probably lead to loss of function, as caused by partial chd2 knockdown that results in markedly enhanced photosensitivity in zebrafish. Together, these data strongly suggest that some human CHD2 mutations cause photosensitivity.

There are potential limitations of our work. Different sequencing platforms were used for the various studied groups. However, we note that all unique variants in cases were confirmed by a second method, whereas for ExAC controls we used a liberal threshold to maximize sensitivity to unique variants, such that a proportion of variants selected from ExAC will be false positive: the net result of this overall conservative approach is only to reduce study power. The ExAC cohort is also the biggest relevant control data set available, and the most likely of any existing data set to provide an accurate estimate of the

Figure 3  Electrographic activity of zebrafish larvae with chd2 knockdown and light ON stimulus. Zebrafish larvae (4 dpf) were kept in the dark (or darkened environment, if not possible otherwise) for all groups in Danieau's medium. Tectal field recordings were performed for the first 5 min in the dark and subsequently in light ON state for the following 5 min in morpholino-injected larvae (n = 15) and non-injected larvae (n = 10). A spiking episode, either spontaneous or evoked by light, was defined as a paroxysm of high-frequency (200–500 Hz) activity with the amplitude exceeding three times the background. Average duration of spiking events ± SEM detected per condition is shown in A. Average number of events per fish ± SEM is shown in B. Cumulative duration of spiking activity per fish as seconds ± SEM is shown in C. Cumulative frequency distribution of spiking episodes is shown in D: morpholino-injected larvae show more activity than any of the non-injected controls, and a higher photosensitivity (curve shift to the right in the light compared to the dark recordings). *P < 0.05 and **P < 0.01 Mann-Whitney test.
true frequency of unique variation in CHD2 in a population not enriched for photosensitive epilepsy. Taking all these factors into account, the use of different platforms is very unlikely to have generated false positive results—indeed, we are more likely to have underestimated unique variant numbers in cases. It is also possible that our choice of statistical test may have missed a true association between rare variation in CHD2 and GGE (irrespective of photoparoxysmal response or photosensitivity), and we did not test whether CHD2 variation contributes to epilepsy more broadly: we therefore cannot exclude the possibility that rare CHD2 variation contributes to epilepsy per se. Lack of parental samples meant we could only confirm variants were de novo in two patients. Family samples were only available in one other case (Case 9): the variant was inherited from a clinically-unaffected mother in whom no EEG studies had been carried out.

Our results provide evidence for a specific gene in a particular trait in epilepsy. Understanding the genetic basis of the photosensitivity trait is a first step to elucidating the biology that underlies photoparoxysmal response and its relation to epilepsy. Human photosensitive epilepsy paradigms have facilitated epilepsy treatment discoveries (French et al., 2014); understanding photoparoxysmal response biology may increase the value of these paradigms. Our findings may also provide new directions for understanding human cortical excitability.

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Supplementary material

Supplementary material is available at Brain online.

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Holger Thiele, Cologne Center for Genomics, University of Cologne, Cologne, Germany; Ingo Helbig, University Medical Center Schleswig-Holstein, Christian-Albrechts University, Kiel, Germany; Janine Altmüller, Cologne Center for Genomics, University of Cologne, Cologne, Germany; Julian Schubert, Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany; Kamel Jabbari, Cologne Center for Genomics, University of Cologne, Cologne, Germany; Kate Everett, Human Genetics Research Centre, St George’s University of London, London, UK; Pasquale Striano, Pediatric Neurology and Muscular Diseases Unit, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, G. Gaslini Institute, Genoa, Italy; Patrick May, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg; Peter Nürnberg, Cologne Center for Genomics, University of Cologne, Cologne, Germany; Center for Molecular Medicine Cologne (CMMC), University of Cologne, Cologne, Germany; Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany; Rikke Møller, Danish Epilepsy Centre, Dianalund, Denmark; Institute for Regional Health Services, University of Southern Denmark, Odense, Denmark; Rima Nabbout, Centre de Reference Epilepsies Rares, Inserm U1129, Neuropediatrics Department, Necker-Enfants Malades Hospital, APHP, Paris Descartes University, CEA, Orsay, France; Roland Krause, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg; Rudi Balling, Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Esch-sur-Alzette, Luxembourg; Stephanie Baulac, Institut National de la Santé et de la Recherche Médicale U975, Centre de Recherche de l’Institut du Cerveau et de la Moelle Epinière, Hôpital Pitié-Salpêtrière, Paris, France; Centre National de la Recherche Scientifique, Centre de Recherche de l’Institut du Cerveau et de la Moelle Epinière, Hôpital Pitié-Salpêtrière, Paris, France; Université Pierre et Marie Curie (Paris VI), UMR_S 975, Paris, France; Thomas Sander, Cologne Center for Genomics, University of Cologne, Cologne, Germany; Wolfram Kunz Department of Epileptology and Life & Brain Center, University of Bonn Medical Center, Bonn, Germany; Yvonne Weber, Department of Neurology and Epileptology, Hertie Institute for Clinical Brain Research, University of Tübingen, Tübingen, Germany.