Detection of nocturnal convulsive seizures using an automatically updated heart rate-based algorithm

Introduction: Automated epileptic seizure detection in a home environment has been of increased interest the last couple of years. One of the options for these algorithms is to use the heart rate in order to detect these seizures automatically. State-of-the-art seizure detectors using the heart rate however cause too many false alarms due to the strong patient-dependency of the heart rate characteristics.

Methods: The proposed heart rate-based algorithm starts as a generic algorithm (with initially mediocre performance), but quickly adapts itself to the patient-specific characteristics as more patient-specific data is obtained in real-time. The algorithm then converges towards a patient-specific optimal performance over time. This is done by using a simplified low-complexity classification method which characterizes normal non-epileptic heart rate behavior, and detects abnormal heart rate behavior as potential seizures.

Results: The algorithm was evaluated on 558 hours of continuous nocturnal ECG data coming from 14 patients with 79 severe convulsive seizures. The algorithm detected on average 87.77% of these seizures. The algorithm can adapt itself automatically to the patient-specific characteristics after on average 5.5 hours, resulting in on average 0.5 false alarms/hour after this initialization phase. This is a reduction of false alarms of at least a factor two compared to generic heart rate-based algorithms from the literature.

Conclusion: Severe convulsive seizures were detected accurately by using the proposed approach. The low-complexity algorithm can be easily implemented in wearable devices for seizure detection at home, which can be used on its own or in addition to accelerometer-based seizure detection.

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ICNC-0203  “Amplitude-integrated EEG with raw trace” compared with “conventional video EEG” for seizure detection in term neonates: a diagnostic accuracy study

Background: Role of amplitude-integrated electroencephalography (aEEG) for detection of neonatal seizures is a topic of debate. Method: A prospective study comparing “aEEG with raw trace” with the “gold-standard” conventional video electroencephalogram (c-VEEG) in term infants at risk of seizures was conducted. Simultaneous recording of aEEG and c-VEEG were done for 24 hours for each infant. “aEEG with raw trace” was interpreted by two neonatal readers; c-VEEG was interpreted by a neurologist independently. Results: Thirty-five infants were enrolled in the study. All seven infants who had seizures on c-VEEG were also diagnosed to have seizures on aEEG, resulting in a sensitivity of 100%. However, seven other infants were incorrectly diagnosed to have seizures on aEEG and hence specificity was 75% (95% CI 59, 91). Among the seven infants with confirmed seizures, there were 169 “individual seizure” episodes, of which only 57 were picked up on aEEG. For the detection of these “individual seizures,” sensitivity and specificity were 33% (95% CI 26, 41) and 70% (95% CI 64, 77) respectively. There was a fair inter-observer agreement between the aEEG readers for detection of individual seizures (Kappa=0.38). Conclusions: aEEG with raw trace” has excellent sensitivity to detect “patients with seizures” but comes with a cost of over-diagnosis. It also failed to identify majority of the “individual seizures”. Therefore, aEEG is a good tool for identifying infants who would benefit from continuous c-VEEG monitoring. aEEG with raw trace cannot be recommended as a mainstay diagnostic tool for continuous monitoring and treatment of neonatal seizures.

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ICNC-0272 Genetic etiologies screening in Chinese infantile spasms of unknown cause

Introduction Infantile spasms (IS) is the most common early-onset epileptic encephalopathy and majority of the patients are caused by genetic etiologies that need further investigation. Methods DNA from 94 patients with unexplained IS was detected for genome-wide copy number variations (CNVs) by single nucleotide polymorphism arrays, then we accomplished the validation and parental resource analyses for patients with significant CNVs. Following that, target region capture sequencing including 308 genes was performed in 36 unsolved patients and whole-exome sequencing in 55 unsolved patients, then we validated the likely pathogenic genes mutations by sanger sequencing in trios. Results Eleven of the 94 patients with IS (11.70%) carried at least one large CNVs more than 1M, including 15q11.2 duplication in 2 cases and a 5p11-p12 duplication contain HCN1 gene. And we identified 11 pathogenic do novo mutations in a total 68 unsolved patients including CDKL5 (in 3 patients), STXBP1 (in 2 patients), DNM1, KCNQ2, SLC35A2, ARX, TSC1, and MLL2. The positive rate of target region capture sequencing chip was 11.11% (4/36) and the whole-exome sequencing was 12.73% (7/55). Conclusion Our study showed the important role of the genetic influence underlying the unexplained IS. Genetic etiologies included large CNVs in 11.70% patients and de novo genes mutations in 16.18% patients. And the whole-exome sequencing still showed the superiority to CNVs analysis and target region capture sequencing though we lacked further analysis of the putative new epilepsy genes in whole-exome sequencing data.

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ICNC-0266  Copy number variation in a hospital-based cohort of children with epilepsy

Introduction. Copy number variants (CNVs), detectable with chromosomal microarray, have been shown to cause or predispose to epilepsy. We evaluated the diagnostic yield of microarray analysis in a hospital-based cohort of children with epilepsy and searched for novel candidate genes or susceptibility loci for epilepsy. Methods. We included all children who presented with seizures in a University Medical Centre between January 2000 and May 2013 and had undergone microarray analysis before May 2014. CNVs of at least three (single nucleotide polymorphism array) or four (oligo array) consecutive probes on chromosome 1-22 or X that were found in <1% of healthy controls and comprised protein-coding genes were evaluated for their pathogenicity. Results. Microarray analysis had been performed in 226 of 1368 (16.5%) children with seizures, all 226 children with a definite diagnosis of epilepsy. In 181 children, 408 CNVs were evaluated for their pathogenicity. Twenty-seven known and clinically relevant CNVs for epilepsy were found in 26 (12%) children. Two-third of these 26 children had focal epilepsy and all 26 had accompanying developmental or behavioural problems. In five children, we found novel CNVs that comprised potential candidate genes for epilepsy: MYT1L, UNC5D, SCN4B and NRXN3 (n=2). Conclusion. We found clinically relevant CNVs in 12% of a selected subgroup of children with epilepsy and identified four novel candidate CNVs for epilepsy. Our results further demonstrate the importance of microarray analysis in epilepsy.

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Heterozygous truncation mutations of the SMC1A gene cause a severe early-onset epilepsy with cluster seizures in females

Introduction: The phenotype of seizure clustering with febrile illnesses in infancy/early childhood is well-recognised. To date the only genetic epilepsy consistently associated with this phenotype is PCDH19, an X-linked disorder restricted to females(1). The SMC1A gene, which encodes a structural component of the cohesin ring, is also carried on the X chromosome. Missense variants and small in frame deletions of SMC1A cause approximately 5% of Cornelia de Lange Syndrome (CdLS). Because SMC1A escapes X-inactivation SMC1A accounts for equal proportions of males and females with CdLS(2). Recently, frameshift and splice site SMC1A mutations have been reported in 2 females with developmental delay and refractory epilepsy(3,4).

Methods: The Deciphering Developmental Disorders (DDD) study invited UK clinicians to refer children with undiagnosed neurodevelopmental disorders. Whole exome sequencing was performed on >4000 children and their parents (trios). 24% of children referred had epilepsy(5).

Findings: 8 patients with de novo mutations in the SMC1A gene were identified. All 8 mutations resulted in truncation of the SMC1A protein. All cases were female, and none had a clinical diagnosis of CdLS. They presented with onset of epileptic seizures between 4 weeks and 28 months of age. In 5/5 cases for whom we presently have detailed phenotypic descriptions, a marked preponderance for seizures to occur in clusters was noted. Seizure clusters were associated with developmental regression, and in all cases moderate or severe developmental delay was apparent.


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Loss of function mutations in SLC12A5 in autosomal recessive epilepsy of infancy with migrating focal seizures

Introduction: Epilepsy of infancy with migrating focal seizures (EIMFS) is a severe pharmacoresistant epilepsy syndrome. Mutations in a number of causative genes, including KCNT1, have been previously reported, and it is clear that EIMFS is genetically heterogeneous. Here we present the first report of mutations in SLC12A5, encoding the potassium chloride co-transporter KCC2, as a recessive cause of EIMFS.

Methods: Two families (each with 2 affected children) were studied using autozygosity mapping and whole exome sequencing strategies. To determine the effects of mutant protein, structural homology modelling, immunoblotting, confocal microscopy and voltage-clamp recording were undertaken. TALEN-mediated genome editing was utilised to generate a double KCC2a-KCC2b knockout zebrafish model.

Results: Genetic investigations revealed compound heterozygous SLC12A5 missense variants in Family 1 (c.1277T>C, L426P; c.1652G>A, G551D) and a homozygous missense variant in Family 2 (c.932T>A, L311H). Protein homology modelling predicted detrimental effects on protein structure and substrate binding. Mutant KCC2 exhibits a depolarised chloride reversal potential and delayed recovery from chloride load. Reduced total and cell surface expression of mutant KCC2 was evident with impaired protein glycosylation. The knockout zebrafish demonstrated abnormal jerky movements on tactile response testing at 2 days post-fertilisation.

Conclusions: We report loss-of-function SLC12A5 mutations in EIMFS. KCC2 plays a fundamental role in fast synaptic inhibition. We show that these EIMFS mutations result in reduced KCC2-mediated chloride extrusion, thereby impairing normal synaptic inhibition and promoting neuronal excitability. Elucidation of novel disease mechanisms is vital to the future development of targeted therapies for these early onset epilepsies.

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A combined metabolomic-genetic approach in early onset epileptic encephalopathies – towards diagnosis and novel biomarker identification

**Background**

Early onset epileptic encephalopathies (EE) represent a heterogeneous group of rare disorders that constitute a major diagnostic and therapeutic challenge. Recent advances in mass spectrometry, next generation sequencing and biostatistical analysis have generated powerful new diagnostic tools. Here, we applied a combined “omics” approach to unravel the etiologic background of early-onset EE in a cohort of 63 patients.

**Methods**

In an interdisciplinary study, we included 63 patients with early onset EE of unclear etiology. Genetic work-up included a high resolution chromosomal microarray and a whole exome sequencing (WES) in index patients and their parents. Neurometabolic analysis comprised plasma aminoacids, alpha-aminoadipic semialdehyde, pipecolic acid, plasma vitamin B6 compounds, a lymphoblast culture and an untargeted metabolomics approach.

**Results**

Clinical and EEG record data were collected from all patients. In 8% (5/63), microarray analysis identified pathogenic deletions (del 1p36, del 22q11.23, del CDKL5/GPM6A, del UBE3A, del MBDS). In 38% (19/49), WES revealed mutations in known EE/ID genes (ARX, CDKL5, FKTN, SCN1A, SCN2A, SCN8A, KCNQ2, SMS, ACO2, KDM5C, STXB1, GABRB2, MIB1), while in 51% (25/49) novel candidate genes are under investigation. Targeted biochemical analysis was normal in all patients. Untargeted metabolomic analysis in 53 patients revealed novel potential plasma biomarkers for Snyder Robinson Syndrome and infantile cerebellar retinal degeneration respectively. An intra-group metabolomics analysis further identified outliers for 6 patients with known mutations, 3 patients with candidate genes and two patients without significant findings in the exome analysis. These data are currently under investigation.

**Conclusion**

A combined omics analysis provides a powerful set of tools to identify and characterize known and novel EE. WES allows to unravel mutations in known but also novel candidate genes. Untargeted metabolome analysis can give evidence for the pathogenicity of novel missense mutations affecting metabolic pathways. Metabolomics further has the ability to identify novel biomarkers that may facilitate diagnosis and future treatment monitoring.