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'North Sea' progressive myoclonus epilepsy: phenotype of subjects with *GOSR2* mutation

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We previously identified a homozygous mutation in the Golgi SNAP receptor complex 2 gene (*GOSR2*) in six patients with progressive myoclonus epilepsy. To define the syndrome better we analysed the clinical and electrophysiological phenotype in 12 patients with *GOSR2* mutations, including six new unrelated subjects. Clinical presentation was remarkably similar with early onset ataxia (average 2 years of age), followed by myoclonic seizures at the average age of 6.5 years. Patients developed multiple seizure types, including generalized tonic clonic seizures, absence seizures and drop attacks. All patients developed scoliosis by adolescence, making this an important diagnostic clue. Additional skeletal deformities were present, including *pes cavus* in four patients and syndactly in two patients. All patients had elevated serum creatine kinase levels (median 734 IU) in the context of normal muscle biopsies. Electroencephalography revealed pronounced generalized spike and wave discharges with

a posterior predominance and photosensitivity in all patients, with focal EEG features seen in seven patients. The disease course showed a relentless decline; patients uniformly became wheelchair bound (mean age 13 years) and four had died during their third or early fourth decade. All 12 cases had the same variant (c.430G>T, G144W) and haplotype analyses confirmed a founder effect. The cases all came from countries bounding the North Sea, extending to the coastal region of Northern Norway. 'North Sea' progressive myoclonus epilepsy has a homogeneous clinical presentation and relentless disease course allowing ready identification from the other progressive myoclonus epilepsies.

Introduction

The progressive myoclonus epilepsies are a group of rare and devastating genetic disorders characterized by myoclonus, generalized tonic clonic seizures and progressive neurological deterioration in the form of ataxia or cognitive dysfunction (Berkovic *et al.*, 1986). They are often refractory to conventional treatment.

Broadly, the progressive myoclonus epilepsies can be divided into two groups: those associated with progressive dementia and those without significant cognitive changes (Hodskins and Yakovlev, 1930; Harriman *et al.*, 1955). Unverricht-Lundborg disease is the prototypical progressive myoclonus epilepsy associated with preserved cognitive function, presenting around the age of 10 years with progressive myoclonus, mild ataxia and generalized tonic clonic seizures (Berkovic *et al.*, 1993). The clinical course varies, although many patients maintain the ability to walk independently for the entirety of their lives (Magaudda *et al.*, 2006). An unstable dodecamer repeat located in the cystatin B (*CSTB*) gene promoter region is the causative mutation in the majority of cases of Unverricht-Lundborg disease (Lalioti *et al.*, 1997).

The arrival of the molecular genetic era has vastly expanded our ability to classify the 'Unverricht-Lundborg-like' progressive myoclonus epilepsies. Several distinct molecular genetic entities with clinical similarity to Unverrict–Lundborg disease have been identified. A founder haplotype on chromosome 12 was identified in Arab subjects from Israel and Jordan that confers a similar phenotype with a slightly more severe clinical course and impaired upgaze; a *PRICKLE1* variant was found but has not yet been replicated in other cohorts (Berkovic *et al.*, 2005; Bassuk *et al.*, 2008). Another subset of patients with an Unverrict–Lundborg disease-like phenotype, with or without associated renal failure, have a recessive disease associated with mutation in the *SCARB2* gene (Berkovic *et al.*, 2008; Dibbens *et al.*, 2009, 2011).

Recently, our group identified another gene responsible for a *CSTB*-negative progressive myoclonus epilepsy with preserved cognitive function (Corbett *et al.*, 2011). The defect is a homozygous c.430G>T transversion in the Golgi SNAP receptor complex 2 gene (*GOSR2*; MIM 604027; NM_004287.3) on chromosome 17, resulting in a p.Gly144Trp (G144W) substitution in a conserved residue in the Qb-SNARE domain. The GOSR2 protein is important in vesicle trafficking from the *cis* to *trans* compartments of the Golgi apparatus (Lowe *et al.*, 1997).

Here we provide a detailed analysis of the clinical phenotype and electrophysiological characteristics of progressive myoclonus epilepsy resulting from a homozygous mutation in *GOSR2*.

Patients and methods

Subjects

We identified 159 patients with confirmed or suspected progressive myoclonus epilepsy, in whom no cause had been found despite appropriate investigations (including *CSTB* gene mutations, *SCARB2* mutations, *PRICKLE* mutations, Lafora bodies, and testing for mitochondrial cytopathies) and screened them for mutations in *GOSR2*. Case 6 was identified following recognition of the clinical pattern and sequencing of *GOSR2* by authors K.M.A., T.P., A.S.P. and M.R. Case 11 was identified by interrogating whole exome data by authors E.J.K. and M.W. For positive cases, we systematically collected clinical data on age of onset of motor symptoms, cognitive decline, age at onset of seizures, seizure types, EEG features, presence of skeletal abnormalities (such as scoliosis), results of available electromyography and nerve conduction studies, highest creatine kinase level, muscle and skin biopsy results. This study was approved by the Ethics Committee at the Austin Hospital (Melbourne, Australia) and written informed consent was obtained from all patients.

GOSR2 gene mutation analysis

GOSR2 mutations were detected by sequencing genomic DNA isolated from patients' peripheral blood using standard methods.

Chromosome 17 haplotype analysis

Microsatellite markers flanking the *GOSR2* gene were selected from the Marshfield human linkage map. Genotyping of individuals with the G144W homozygous mutation was performed using the QIAGEN Multiplex kit (Catalogue no 206143) to amplify and an ABI Prism 3130 DNA Analyzer (Applied Biosystems) to analyse products.

Estimation of the age of the mutation

Shared ancestral haplotype lengths for 10 of the unrelated individuals (ignoring one of the siblings from Family 5 and excluding Patient 11) were inferred from the microsatellite marker data in Fig. 1 based on the deCode genetic map, taking into account the non-uniformity of the marker data (Kong *et al.*, 2002). The age of the mutation was estimated using the same methodology as described in Corbett *et al.* (2011), assuming independent recombination histories for each individual.

Results

We identified 12 affected subjects from 11 families with mutations in *GOSR2*. Two individuals from Family 5 were a sibling pair. Six

Figure 1 Haplotype sharing between 10 affected families showing a *GOSR2* founder mutation. Analysis of microsatellite markers spanning 6.7 Mb around *GOSR2* are shown. Markers that were inferred to be part of the shared haplotype are shown in red. Note that marker *D17S806* has been added to those shown in our earlier article (Corbett *et al.*, 2011). For marker *D17S806* the shared haplotype in Patients 2–10 was 168 bp in length while in Patient 1 this marker was 166 bp in length, which is likely due to ancestral contraction of this microsatellite, since the next shared marker (*D17S1785*) was identical in all cases.

subjects were briefly described earlier (Corbett *et al.*, 2011), and six new unrelated cases were subsequently found. All 12 cases had an identical homozygous 430G-T transversion in *GOSR2*, resulting in a p.Gly144Trp (G144W) substitution in a conserved residue in the Qb-SNARE domain. Haplotype analysis using highly polymorphic microsatellite markers surrounding the *GOSR2* mutation showed a shared haplotype on chromosome 17 (Fig. 1) suggesting the patients have a common ancestry. Other *GOSR2* gene variants that were detected in our analysis included the single nucleotide polymorphisms (SNPs) c.7 C>A, P3T (rs12944167), c.200G>A, R67K (rs197922) and the intronic variant (rs189899). We also detected two previously unreported synonymous rare variants c.111C>T, p.I37I and c.612 C>T, p.H204H, each observed at an allele frequency <1% in our patient cohort (Supplementary Fig. 1).

Estimation of the age of the mutation

Shared ancestral haplotype segments of 0.42, 2.76, 0.23, 0.23, 0.42, 0.77, 0.23, 0.23, 1.55 and 2.76 cM were estimated from Patients 1 to 10, respectively, using the deCode genetic map (Supplementary Fig. 2). These data led to an age estimate of 180 generations for the *GOSR2* mutation with a 95% confidence interval of (121, 293) generations. Assuming that one generation corresponds to 20 years leads to an age estimate for the mutation of 3600 years with a 95% confidence interval of (2420, 5860) years.

Clinical genetic analysis

Consanguinity was documented in three patients. The parents of Patient 1 were second cousins, and the parents of Patient 6 were second cousins once removed (the father's paternal grandfather and maternal grandfather's maternal grandfather were brothers). Also, the paternal grandfather and maternal grandmother of Patient 10 were first cousins and his paternal grandfather and paternal grandmother are also first cousins. The parents of Patient 3 were not known to be related, although they are from the same small village in the northern part of The Netherlands. Remarkably, the birthplaces of the parents (or great-great grandparents for the maternal and paternal side for Patient 1 from Australia) were clustered around the North Sea extending to the coastal region of Northern Norway (Fig. 2).

Seizure types and onset

Myoclonic seizures were the first seizure type in 10 of 12 cases. Patient 6 had a febrile seizure at the age of 14 months, and Patient 10 had absence and generalized tonic clonic seizures before myoclonus was recognized. Myoclonus began on average at age 6.5 years (range 4–12 years; see Table 1 for a summary of clinical findings). All patients experience severe, highly photosensitive generalized myoclonus that worsened with action or with emotional stressors. It was minimal at rest and almost completely absent during relaxation. On action, myoclonus affected the
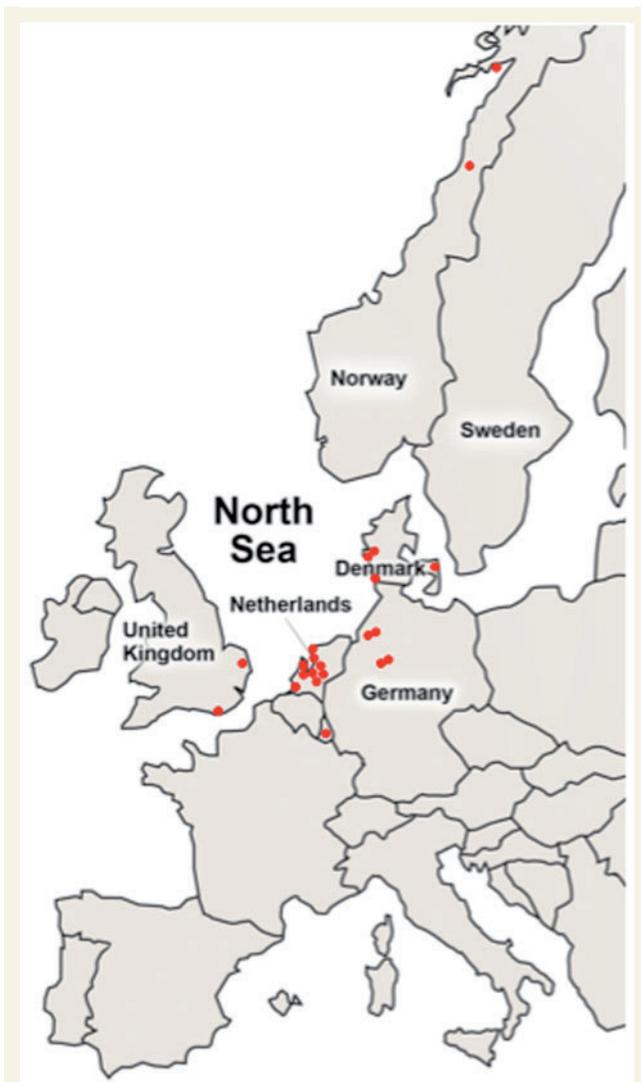
Figure 2 Map of the distribution of 'North Sea' progressive myoclonus epilepsy. The red dots indicate the birthplaces of the parents (or great-grandparent in the case of the Australian patient originating from UK descendants) of patients with progressive myoclonus epilepsy due to a homozygous mutation in *GOSR2*.

moving limb with involvement of adjacent portions of the body, as well as movement sometimes inducing generalized myoclonus. In some patients there was clinical evidence of negative myoclonus, but this was not formally documented electrophysiologically. Patient 2 experienced periods of 'status myoclonicus' characterized by continuous myoclonus for hours to a day at a time. She also exhibited exacerbation during sleep. Patient 6 had nightly periods of continuous clinical and electrographic myoclonus. Patients 1, 2, 4 and 7 had drop attacks beginning around the age of 13 or 14 years. Generalized tonic clonic seizures were documented in all except Patient 2. The average age of onset of generalized tonic clonic seizures was 13.3 years (range 3–24 years; Table 1). Absence seizures were present in six patients (Patients 1, 4, 5b, 7, 8 and 10).

Neurological findings

The clinical pattern was remarkably uniform with ataxia being the first definite feature; mean onset age of 2.3 years (range 1–3.5 years; Table 1). Areflexia was documented in 9 of 12 patients, and hypotonia in 7 of 12 patients identified from birth to early childhood. Patients 2 and 6 were noted to be hypotonic at birth and Patients 6 and 8 had difficulty feeding in infancy. Motor development was delayed in some patients before age 2 years, manifesting as delayed walking. Patients 3 and 6 walked at 18 months, Patient 5a walked at 21 months, Patient 9 walked at 29 months and Patient 10 walked at 24 months.

Patient 9 had left optic atrophy. Other neurological findings, such as hearing loss, retinal abnormalities, sensory impairment, pyramidal or extrapyramidal signs, were absent.

Cognitive function

There was a notable preservation of cognition in the context of severe motor disability until late in the course of the disease. All patients attended normal schools until their physical limitations prohibited them from doing so. The lowest cognitive performance was documented in Patient 7, whose verbal IQ was 75 as measured by the Wisconsin Intelligence Scale for Children. Unlike the other patients, he was said to have mild intellectual disability for his entire life. This is in contrast to Patient 2, with a verbal IQ of 113. All performance IQs were confounded by profound motor dysfunction.

Patient 1 had mild memory dysfunction that began at 25 years of age, followed by emotional lability in the last year of her life. Patient 4 had emotional lability and memory decline beginning at age 25 years. Patient 5a was noted to have mild cognitive decline in the last year of her life, whereas her brother, Patient 5b had no cognitive dysfunction at age 28 years, the year prior to his death. Patient 8 experienced a mild cognitive decline in his early 20s, a few years before his death.

Other clinical features

Scoliosis was present in all 12 patients and was typically documented between the ages of 8 and 14 years. The range of severity varied. Some patients required surgical intervention with Harrington rods whereas in others, the scoliosis was mild. Other skeletal deformities were found, including *pes cavus* in four patients and syndactyly in two patients. Patient 6 had thickened webbing between the second and third toes. Delayed puberty was documented in two patients (Patients 7 and 9), and Patient 3 had irregular menses and premature ovarian failure at the age of 30.

Therapy

All patients were on multiple anti-epileptic medications. To our knowledge, none were treated with phenytoin, as many had the presumed diagnosis of Unverrict–Lundborg disease, even in the absence of the known mutations. Five patients were treated with valproic acid (Patients 1, 4, 6, 7, 10). Patient 1 experienced no benefit on this medication, while Patient 6 experienced significant worsening of ataxia. Many patients experienced significant seizure reduction from levetiracetam (Patients 2, 4 and 7) and/or zonisamide

Table 1 'North Sea' progressive myoclonus epilepsy clinical characteristics and seizure types

Patient	Age	Nationality	Ataxia	Seizure types (age of onset)	Skeletal findings	Highest creatine kinase (IU)	Current status
1 (F)	32	Australian (UK origin)	2	Myoclonus 8 GTCS 13 Absence 7 Drop attacks 13	Scoliosis Pes cavus	800	Wheelchair bound 14 Dysphagia 27 requiring PEG Bed bound 32 Deceased 32 aspiration Pneumonia
2 (F)	17	German	1	Myoclonus 6 Status myoclonicus Nocturnal myoclonus Drop attacks 13	Scoliosis	580	Wheelchair bound 8
3 (F)	32	Dutch	3	Myoclonus 6 GTCS 14	Scoliosis Syndactyly	267	Wheelchair bound 13 Dysphagia 30 Bed bound 32
4 (F)	30	Dutch	2	Myoclonus 10 GTCS 12 Absence 6 Drop attacks 14	Scoliosis Syndactyly	800	Wheelchair bound 27
5a (F)	24	Dutch	2	Myoclonus 6 GTCS 21	Scoliosis	668	Wheelchair bound 10 Dysphagia 24 Deceased 24 respiratory complications
5b (M)	29	Dutch	2	Myoclonus 5 GTCS 24 Absence 24	Scoliosis	213	Wheelchair bound 12 Dysphagia 24 Deceased 29 respiratory complications
6 (M)	10	Norwegian	1	Myoclonus 4.5 Nocturnal status myoclonica GTCS 8.5 FC 14 months	Scoliosis Thickened webbing between second and third toe	1135	Wheelchair bound 11
7 (M)	29	Danish	3	Myoclonus 5 GTCS 21 Absence 7 Drop attacks during fever 2 Atypical absence 2	Scoliosis *Pes cavus*	2360	Wheelchair bound 10 Dysphagia 24 PEG 26 Respirator dependent
8 (M)	27	Dutch	3.5	Myoclonus 4 GTCS 8 Absence 5	Scoliosis	2467	Wheelchair bound 10 Dysphagia 25 Deceased 27 status epilepticus
9 (F)	18	German	2	Myoclonus 6 GTCS 10 Drop attacks	Scoliosis Pes cavus	500	Wheelchair bound 14
10 (M)	37	Danish	3	Myoclonus 12 GTCS 3 Absence 3 Drop attacks 3	Scoliosis	391	Wheelchair bound 14 Dysphagia 26
11 (F)	13	Dutch	2.3	Myoclonus 6 GTCS 12	Scoliosis Pes cavus	989	Wheelchair bound 10 Dysphagia early childhood

Onset age (in years) of motor dysfunction, seizure type and wheelchair dependence of patients with 'North Sea' progressive myoclonus epilepsy.
GTCS = generalized tonic clonic seizures; FC = febrile convulsion.
Some of the values obtained for Patients 1–5b were briefly described previously (Corbett *et al.*, 2011).

(Patients 1, 6 and 7) but systematic evaluation of therapeutic responses was not possible with cross-sectional ascertainment.

Clinical course

Independent ambulation was impaired relatively early in the disease course. Patients became wheelchair bound at a mean age of 13 years (range 8–27 years). While patients maintained motor strength, ataxia and severe stimulus sensitive myoclonus appear to be the predominant reason for loss of independent ambulation.

Fever and infectious disease had a notable impact on the clinical findings in seven patients (Patients 2, 4, 5a, 6, 7, 9 and 11). The ataxia in Patient 4 was initially diagnosed as presumed acute viral cerebellitis at the age of 2. The diagnosis was revisited and

thought to be an acute exacerbation of a chronic process when her symptoms returned and worsened between the ages of 4 and 7 years. Patient 5a had a decline in motor milestones following a febrile illness at the age of 8 months. Myoclonus in Patients 2, 7, 9 and 11 were significantly worse with fever and Patient 7 had drop attacks during febrile illness. Patient 6 experienced ataxia following a febrile convulsion at the age of 14 months.

Seven patients (Patients 1, 3, 5a, 5b, 7, 8 and 10) developed dysarthria and dysphagia in their mid- to late 20's (range 24–30 years). Patient 11 developed dysarthria and dysphagia in early childhood. Patients 1, 3 and 7 required PEG placement to assist with feeding. Patient 7 has respiratory compromise and now requires chronic ventilator assistance.

At last evaluation, the patients ranged in age from 11 to 37 years (Table 1) and four were deceased. The cause of death (age range 24–32 years) involved respiratory compromise, aspiration pneumonia or status epilepticus.

Electroencephalography

All patients displayed generalized spike and slow wave discharges with a posterior predominance (Fig. 3) often with a slow background, findings reminiscent of other progressive myoclonus epilepsies (Berkovic et al., 1991). The generalized discharges were highly photosensitive. Focal or multifocal discharges were documented in seven patients (Fig. 4A–C). Patient 6 had focal bitemporal and occipital spike and slow wave discharges that were more prominent during sleep (Fig. 4A). Patient 7 had focal bifrontal-central spike and slow wave discharges (Fig. 4B), independent left then right frontal central spike and slow wave discharges,

and multifocal slow spike and wave complexes. Patient 10 had focal left frontal spike and slow wave discharges (Fig. 4C) and right parietal spikes. Patient 4 had independent occipital, parietal, and temporal spike and wave complexes as well as focal vertex spikes during photic stimulation. Patient 8 had multifocal spike and wave discharges. Patients 9 and 11 had focal bitemporal or bioccipital spike and slow wave discharges. In some patients, the spike and wave bursts were exacerbated by sleep and photic stimulation. A polygraphic recording was performed for Patient 3. This showed a time-locked association between the myoclonic jerks documented by surface electromyography recordings with epileptiform discharges on EEG [see Supplementary Fig. 5 in Corbett et al. (2011)].

Serum creatine kinase and muscle biopsy

There was a persistent mild elevation of creatine kinase in the absence of detectable muscle pathology. All patients had chronically elevated serum creatine kinase (median 734 IU), ranging from 213 IU to 2467 IU. Interestingly, Patient 6's mother noted that the only time period his levels were normal was when he was placed briefly on corticosteroid treatment. This transiently improved his seizures and ataxia, which then returned. Muscle biopsy results were available for all patients except for Patient 5a. The majority of patients had normal biopsy results; neuronal inclusions, Lafora bodies and ragged red fibres were absent. Patient 1 had an unremarkable routine biopsy with a single focus of perivascular lymphocytes, and additional electron microscopy in 1998.
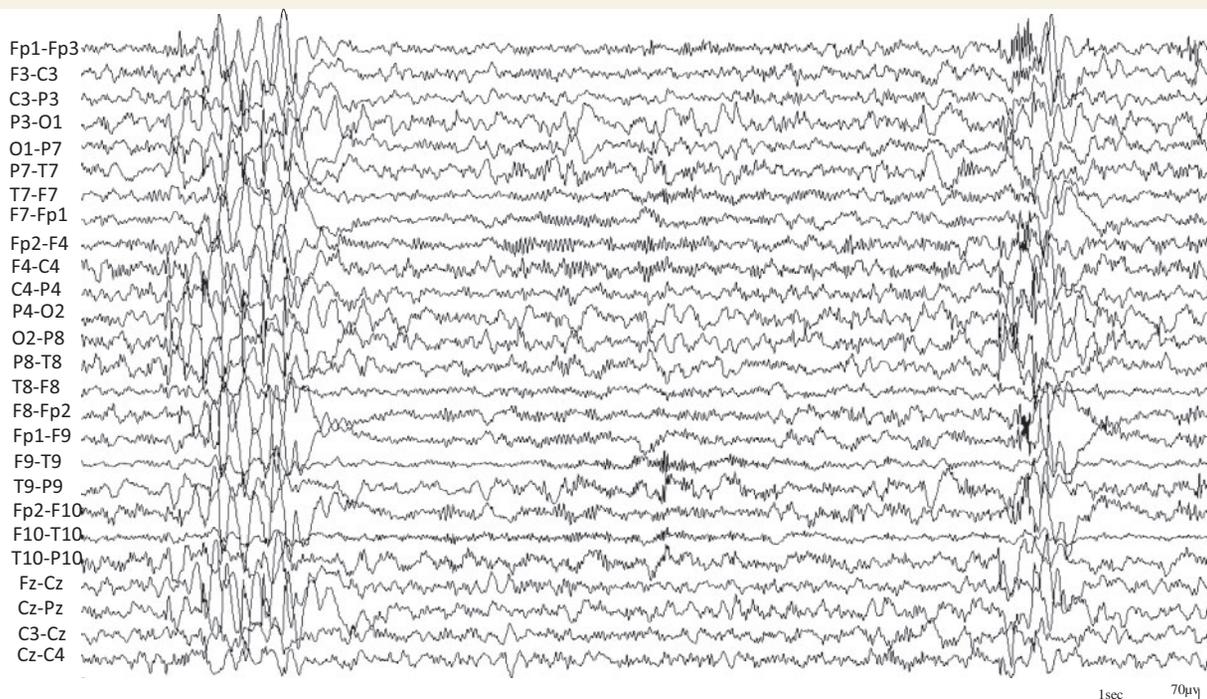
Figure 3 EEG showing generalized epileptiform discharges on a slow background. EEG from Patient 6 (bipolar montage) showing generalized spike and slow wave discharges with an occipital predominance on a slow background.
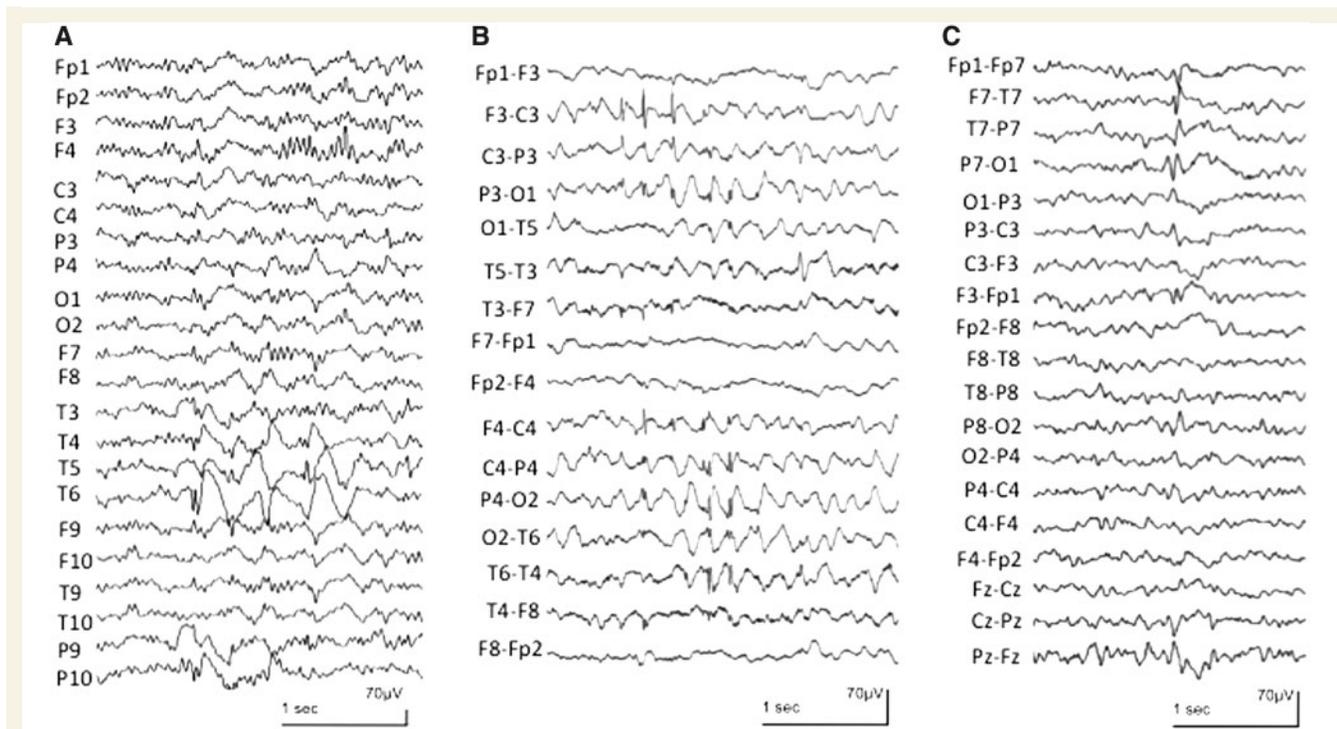
Figure 4 EEGs showing focal epileptiform discharges. (**A**) Patient 6 (source montage) showing independent right and left focal temporal spike and slow wave discharges. (**B**) Patient 7 (bipolar montage) showing independent left then right frontal central spike and slow wave discharges. (**C**) Patient 10 (bipolar montage) showing focal left frontal spike and slow wave discharges.

Subsequent biopsy material taken at autopsy was normal, without evidence of ragged red fibres. There were subsarcolemmal collections of mitochondria, a non-specific finding, and normal Golgi morphology on electron microscopy (data not shown). Patient 2 had vacuolated mitochondria and reduced complex III levels. Patient 6 also had subsarcolemmal collections of mitochondria without paracrystalline inclusions. Aside from these minor findings, the muscle biopsies were consistently normal in the context of chronic mild creatine kinase elevation.

Electrophysiologic studies of the peripheral nervous system

All patients except Patient 5b had needle electromyography and nerve conduction studies. The nerve conduction studies performed on Patients 1, 3, 8 and 9 suggested a mild predominantly axonal peripheral neuropathy, although testing was technically challenging due to frequent myoclonus. Electromyography was normal in all cases except in Patient 1. Findings consistent with a subtle myopathy (presumed to be inflammatory based on a subsequent muscle biopsy) was present on the patient's first study performed in 1988 although a repeat study performed in 2002 was normal, though marred by movement artefact. Somatosensory evoked potentials were obtained in all patients except Patients 5a, 5b, 7 and 11 and were unremarkable. Auditory evoked potentials in Patients 1, 3, 6 and 8 were normal, as were the visual evoked potentials of Patients 1 and 8, as well as electroretinograms of Patients 3 and 7.

Brain magnetic resonance imaging

MRIs were available in all patients and were essentially normal. Patient 4 had mild atrophy of the cerebellar vermis, and Patient 10 had asymmetric cerebral and cerebellar atrophy. The remainder of the MRIs were otherwise unremarkable.

Discussion

Here we describe the clinical and electrophysiological characteristics of progressive myoclonus epilepsy caused by homozygous mutation of the *GOSR2* gene. In addition to the hallmarks of progressive myoclonus epilepsy, this clinical entity is characterized by a highly homogeneous pattern of early onset ataxia, areflexia, scoliosis, elevated creatine kinase levels and relative preservation of cognitive function until late in the disease course.

All 12 cases had an identical homozygous 430G–T transversion in the Golgi SNAP receptor complex 2 gene (*GOSR2*), resulting in a Gly144-to-Trp (G144W) substitution in a conserved residue in the Qb-SNARE domain. No other mutations causing progressive myoclonus epilepsy have yet been discovered in the *GOSR2* gene. Interestingly, the birthplaces of all patients, including the birthplaces of the ancestors of the Australian patient, cluster around the North Sea. The Norwegian patient's family is from an area of Norway that borders the Norwegian Sea, although it is contiguous with the North Sea; hence our use of the term 'North Sea progressive myoclonus epilepsy'. Comparison of haplotypes in patients with the G144W mutation showed that 10 families shared a

common homozygous haplotype, although the extent of homozygosity varied between the families (Fig. 2). Previously, based on haplotype analyses in five families, we estimated that this mutation arose in the European population ~181 generations ago (~3660 years) (Corbett *et al.*, 2011). Repeating this analysis using 10 cases yields an updated estimate of 180 generations, which is very close to the previous estimate, but with a reduced 95% confidence interval of (121, 293) generations when compared with the original confidence interval of (96, 343) presented in Corbett *et al.* (2011). This is because of the increase in sample size from 5 to 10 individuals. The geographic distribution of cases suggests that it may have spread along the North Sea at the time of the Viking conquests in the 8th century; however, the dating of the mutation age indicates that the mutation arose much earlier than the Viking conquests themselves.

Unverricht–Lundborg disease (EPM1, MIM 254800) is the prototypic autosomal recessive progressive myoclonus epilepsy associated with preservation of cognitive function and is due to a mutation in the *CSTB* gene that encodes cystatin B on chromosome 21. While ataxia is a late and mild manifestation of Unverrict–Lundborg disease (Kälviäinen *et al.*, 2008), patients with 'North Sea' progressive myoclonus epilepsy present with early onset ataxia around the age of 2 years. Myoclonus is a prominent manifestation that began around the age of 6–7 years of age in our patient cohort, appearing slightly earlier than the average age of 12–13 years in Unverrict–Lundborg disease. Generalized tonic clonic seizures appear to start at a similar age, ~13 years in both groups (Berkovic *et al.*, 1991; Magaudda *et al.*, 2006). Unverrict–Lundborg disease is characterized by progressive worsening of seizures and myoclonus 5–10 years after clinical onset, followed by a stabilization period (Magaudda *et al.*, 2006). In contrast, patients with 'North Sea' progressive myoclonus epilepsy experienced a period of rapid progression between the ages of 6–10 years of age, followed by a slow and progressive decline.

This form of progressive myoclonus epilepsy has a more precipitous disease course than classical Unverrict–Lundborg disease. Unlike patients with Unverrict–Lundborg disease, who may maintain independent mobility 30 years after disease onset (Magaudda *et al.*, 2006), our 12 patients with 'North Sea' progressive myoclonus epilepsy were wheelchair bound by the age of 13 years. At the time of this study, 4 of 12 of our patients with 'North Sea' progressive myoclonus epilepsy were deceased at an average age of 28 years, whereas many patients with Unverrict–Lundborg disease live 30 years after disease onset (Chew *et al.*, 2008). In a study that followed a cohort of 20 patients with Unverrict–Lundborg disease for 25 years following initial diagnosis, no patients died within that time period (Magaudda *et al.*, 2006). In fact, life expectancy often approaches normal in patients with Unverrict–Lundborg disease (Kälviäinen *et al.*, 2008).

Much like Unverrict–Lundborg disease, in 'North Sea' progressive myoclonus epilepsy there is relative preservation of cognitive function in the presence of severe neurological dysfunction in other spheres. This is also in the context of a paucity of brain abnormalities on MRI and on post-mortem brain examination. As previously reported (Corbett *et al.*, 2011), post-mortem brain tissue from Patient 1 revealed only mild generalized cerebral atrophy and no specific histological abnormality.

To date, 'North Sea' progressive myoclonus epilepsy is the only known form of progressive myoclonus epilepsy to be associated with scoliosis. The neurological underpinnings of scoliosis are not well understood. There is evidence that mutations in the pathways involved in the 'segmentation clock', the signalling circuits that synchronize gene expression cycles in somites during development, may result in scoliosis (Pourquie 2011). There is no direct evidence that *GOSR2* interacts with the genes involved in these pathways such as Notch, *FGF*, or wnt/ß-catenin. This is an area where the cellular mechanisms by which *GOSR2* affects the developing musculoskeletal system require further study.

Progressive myoclonus epilepsy due to a mutation in *GOSR2* may be clinically difficult to distinguish from myoclonic epilepsy with ragged red fibres, especially in the context of an elevated creatine kinase, where subtle or overt muscle involvement is common. The mechanism of raised creatine kinase in subjects with *GOSR2* mutations is unclear and electromyography and muscle biopsies were unremarkable. There is no evidence that repetitive muscle activity from frequent myoclonus causes elevation of serum creatine kinase levels. Raised creatine kinase is not a feature of other progressive myoclonus epilepsies without a myopathic component, where myoclonus is also a continuous occurrence (Erol *et al.*, 2009). The only notable exception is when patients with progressive myoclonus epilepsy experience status epilepticus, specifically following prolonged generalized tonic clonic seizures (Striano *et al.*, 2009). The clinical similarity with other neurological illnesses associated with mitochondrial dysfunction, such as myoclonic epilepsy with ragged red fibres and Friedrich's ataxia, may suggest that the GOSR2 protein is involved in mitochondrial function to some degree although this requires further investigation at the molecular level.

EEG changes such as generalized spike wave discharges on a background of occipital predominant slowing are consistent with the diagnosis of progressive myoclonus epilepsy (Berkovic *et al.*, 1991). Patients with 'North Sea' progressive myoclonus epilepsy seem to be more photosensitive than patients with Unverrict–Lundborg disease, although they lack the extreme photosensitivity of some patients with a mutation in *SCARB2* (Rubboli *et al.*, 2011).

Focal EEG discharges were documented in 4 of 11 patients. Focal or multifocal discharges are rarely reported in Unverrict–Lundborg disease (Westmoreland *et al.*, 1979; Magaudda *et al.*, 2006; Kälviäinen *et al.*, 2008). They can be a feature of Lafora disease, where focal occipital discharges are classically reported (Roger *et al.*, 1983). Other progressive myoclonus epilepsies with focal discharges include myoclonic epilepsy with ragged red fibres, neuronal ceroid lipofuscinosis, and juvenile neuroaxonal dystrophy (Westmoreland *et al.*, 1979; So *et al.*, 1989; Striano *et al.*, 2007). In Unverrict–Lundborg disease, EEG abnormalities tend to stabilize over time, without a significant deterioration of the background, and occasionally even show a reduction in photoparoxysmal response (Magaudda *et al.*, 2006; Ferlazzo *et al.*, 2007). With such a small patient group to draw from, we could not clearly identify progression of EEG findings in 'North Sea' progressive myoclonus epilepsy over time. There was a general sense that myoclonic seizures and associated discharges became more frequent and more stimulus sensitive, with a worsening of background slowing, although a larger collection of patients would be

required to definitively answer this question in the future. Further elucidation of the electrophysiological features with serial polygraphic EEG-EMG recordings, somatosensory evoked potentials and long loop reflexes would also be of value.

Here we describe the clinical and electrophysiological hallmarks of progressive myoclonus epilepsy due to a homozygous mutation in *GOSR2*, which we have termed 'North Sea' progressive myoclonus epilepsy due to the proximity of the patient families to the shores of the North Sea. The disorder appears to have arisen as a founder mutation in Northern Europe. Despite extensive screening of a large cohort of unsolved progressive myoclonus epilepsy cases, we found no cases that were not traceable to the North Sea region and no other mutation apart from G144W. The phenotype is characteristic and clinically recognizable, with early onset ataxia, areflexia, scoliosis and elevated creatine kinase. It illustrates the further molecular dissection of the 'Unverrict–Lundborg disease-like' progressive myoclonus epilepsies, which is essential for clinical and molecular prognostication and genetic counselling.

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Supplementary material

Supplementary material is available at *Brain* online.

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