Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort

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Epilepsy is common in early childhood. In this age group it is associated with high rates of therapy-resistance, and with cognitive, motor, and behavioural comorbidity. A large number of genes, with wide ranging functions, are implicated in its aetiology, especially in those with therapy-resistant seizures. Identifying the more common single-gene epilepsies will aid in targeting resources, the prioritization of diagnostic testing and development of precision therapy. Previous studies of genetic testing in epilepsy have not been prospective and population-based. Therefore, the population-incidence of common genetic epilepsies remains unknown. The objective of this study was to describe the incidence and phenotypic spectrum of the most common single-gene epilepsies in young children, and to calculate what proportion are amenable to precision therapy. This was a prospective national epidemiological cohort study. All children presenting with epilepsy before 36 months of age were eligible. Children presenting with recurrent prolonged (>10 min) febrile seizures; febrile or afebrile status epilepticus (>30 min); or with clusters of two or more febrile or afebrile seizures within a 24-h period were also eligible. Participants were recruited from all 20 regional paediatric departments and four tertiary children’s hospitals in Scotland over a 3-year period. DNA samples were tested on a custom-designed 104-gene epilepsy panel. Detailed clinical information was systematically gathered at initial presentation and during follow-up. Clinical and genetic data were reviewed by a multidisciplinary team of clinicians and genetic scientists. The pathogenic significance of the genetic variants was assessed in accordance with the guidelines of UK Association of Clinical Genetic Science (ACGS). Of the 343 patients who met inclusion criteria, 333 completed genetic testing, and 80/333 (24%) had a diagnostic genetic finding. The overall estimated annual incidence of single-gene epilepsies in this well-defined population was 1 per 2120 live births (47.2/100 000; 95% confidence interval 36.9–57.5). PRRT2 was the most common single-gene epilepsy with an incidence of 1 per 9970 live births (10.0/100 000; 95% confidence interval 5.26–14.8) followed by SCN1A: 1 per 12 200 (8.26/100 000; 95% confidence interval 3.93–12.6); KCNQ2: 1 per 17 000 (5.89/100 000; 95% confidence interval 2.24–9.56) and SLC2A1: 1 per 24 300 (4.13/100 000; 95% confidence interval 1.07–7.19). Presentation before the age of 6 months, and presentation with afebrile focal seizures were significantly associated with genetic diagnosis. Single-gene disorders accounted for a quarter of the seizure disorders in this cohort. Genetic testing is recommended to identify children who may benefit from precision treatment and should be mainstream practice in early childhood onset epilepsy.
Introduction

It is estimated that the lifetime prevalence of epilepsy is 7.60 per 1000 individuals (Fiest et al., 2017) and that 50–65 million individuals are affected worldwide (Ngugi et al., 2010; Fiest et al., 2017). Epilepsy incidence is age-dependent, with the highest incidences (>60 per 100,000) found in those under the age of 5 years and those over the age of 65 years (Hauser et al., 1993). Even in high resource health systems, seizure control is not achieved for one-third of subjects (Kwan and Brodie, 2000).

Children presenting with epilepsy before the age of 3 years experience a high burden of cognitive and behavioural comorbidity (Berg et al., 2008). Comorbidities are more prevalent among children who develop drug-resistant seizures (Wirrell et al., 2012) and those with a high seizure burden (Berg et al., 2012; Wilson et al., 2012). The concept of the ‘developmental and epileptic encephalopathy’ (DEE) recognizes that in children presenting with early-onset epilepsy, neurodevelopmental comorbidity may be attributable to both the underlying cause and to the detrimental effects of uncontrolled epileptic activity (Scheffer et al., 2017). Single-gene causes of childhood-onset epilepsy, such as Dravet syndrome due to SCN1A mutations, typify this concept. Families affected by, and clinicians treating, such epilepsies strive for therapies that more precisely target the syndrome and/or the underlying disease mechanisms, in the hope that seizure control and developmental comorbidity can be simultaneously addressed. Precision therapy approaches have driven randomized therapeutic trials including stiripentol (Chiron et al., 2000) and cannabidiol (Devinsky et al., 2017) in Dravet syndrome, and quinidine in KCNT1-associated epilepsy (Mullen et al., 2018).

The application of next generation sequencing (NGS) technology has facilitated a fundamental change in aetiological diagnosis of epilepsy. When cohorts of children with a suspected genetic cause are tested using NGS, between 18% and 48% receive a diagnosis. The variation in yield may be explained by differences in case inclusion, testing methodology, and number of genes tested (Lemke et al., 2012; Appenzeller et al., 2014; Helbig et al., 2016; Trump et al., 2016; Lindy et al., 2018). Patients included in such studies may have been selected on the basis of the nature of the epilepsy and/or a suspected genetic aetiology. Therefore, these studies may misrepresent the incidence and phenotypic spectrum of the single-gene epilepsies. To appreciate the scope for genetically-guided precision medicine in childhood-onset epilepsy, and to prioritize therapy development, we must understand the epidemiology. This demands a prospective population-based approach to genetic testing.

Materials and methods

Cohort recruitment

Participants were recruited from all 20 regional paediatric departments and four tertiary children’s hospitals in Scotland, from 8 May 2014 to 7 May 2017. Only children who met the inclusion criteria during this period, and who were under 36 months of age, were included.

Inclusion criteria were any of: (i) child receiving a new diagnosis of epilepsy (recurrent unprovoked seizures); (ii) child presenting with an episode of febrile or afebrile status epilepticus (seizure >30 min); (iii) child presenting with two or more febrile or afebrile epileptic seizures within a 24-h period; and
(iv) child presenting with a second prolonged (>10 min) febrile seizure, over any time period.

Patients were excluded if an aetiology that would fully explain seizures was identified either prior to or at first presentation with seizures. Examples of such aetiologies were meningitis, hypoxic ischaemic encephalopathy in the neonate, or focal seizures in an infant with a perinatal stroke.

Children presenting with prolonged and clustering febrile seizures were included because in certain genetic epilepsies, including those associated with SCN1A, PCDH19 and PRRT2 variants, epilepsy can be preceded by febrile seizures (Brunklaus et al., 2012; Figurashi et al., 2013; Ebrahimi-Fakhari et al., 2015). Our aim was to optimize case identification and avoid any delay in genetic diagnosis. Early genetic diagnosis may inform treatment and potentially alter disease course (Brunklaus et al., 2013; Lange et al., 2018).

Maximum case ascertainment was ensured by weekly e-mail reminders throughout the study period to the eight paediatric neurophysiology departments, a link clinician in each of the 24 centres and all 17 epilepsy specialist nurses in Scotland. Research nurses throughout Scotland reviewed admissions to intensive care and high dependency units; and a national continuing education program maintained the profile of the study.

We are not aware of any private medical services in Scotland where young children would present with seizures, and given the geographical location of hospitals in the border regions of England and Scotland we would expect that children in Scotland would access both paediatric and paediatric neurology services from hospitals of the Scottish National Health Service (NHS).

Denominator data for births over the study period were taken from National Records of Scotland birth records (National Records of Scotland, 2018). Incidence estimates were rounded to three significant figures and 95% confidence intervals (CIs) were calculated using the Poisson distribution.

**Genetic testing**

DNA was extracted from whole blood and tested on a custom designed 104 gene epilepsy panel (Supplementary material, part C) at the Scottish Genetic Epilepsy service in Glasgow, unless a genetic diagnosis had already been made through single-gene testing. Accelerated single-gene testing [Sanger sequencing and multiplex ligation probe amplification (MLPA)] of 10 genes (Supplementary material, part D) was offered, with clinicians advised to request these prior to panel testing if clinically indicated. The gene panel was designed to include the early onset childhood genetic epilepsies for which brain imaging was unlikely to give a diagnosis and for which there is evidence for specific therapeutic approaches. Genes to be included on the panel were selected by a team of clinicians (J.D.S., S.M.Z., S.J., D.T.P.) who reviewed the literature extensively. All potentially causative variants identified were validated through Sanger sequencing. Cases negative on the 104 gene panel with typical phenotypes for epilepsy related to SCN1A, KCNQ2, SLC2A1, PCDH19, CDKL5, or MECP2 underwent dosage analysis through MLPA of the relevant gene. All variants of uncertain significance and likely pathogenic/pathogenic variants were discussed in the context of the clinical phenotype by a multidisciplinary team of paediatric neurologists, clinical geneticists and molecular geneticists. Variants were reported with reference to UK Association of Clinical Genetic Science (ACGS) guidelines (Association for Clinical Genetic Science, 2017). Pathogenic and likely pathogenic results were considered diagnostic. Where DNA samples and/or phenotype details from other family members were considered relevant to variant interpretation these were requested. Chromosomal microarray studies were not routinely performed because results were not thought likely to guide therapeutic management.

**Clinical information**

At the time of case recruitment, clinicians completed a structured proforma detailing clinical features and investigation findings (Supplementary material, part E). A panel of three paediatric neurologists reviewed clinical details of all cases to ensure eligibility criteria were met. A minimum of 12 months after initial presentation and 6 months after the recruiting clinician had been informed of the final genetic test result, clinicians completed a structured clinical follow-up questionnaire (Supplementary material, part F). For the purposes of this study, therapy-resistant seizures were defined as ongoing epileptic seizures (one or more seizure per 6 months) despite adequate trials of two or more appropriately chosen, appropriately dosed (or administered) and taken antiepileptic therapies (including non-drug therapies such ketogenic diet and vagus nerve stimulation). The study was approved by the United Kingdom NHS National Research Ethics Service.

**Statistical analysis**

IBM® SPSS® Statistics Version 24 was used to determine associations between clinical features and identification of a genetic cause. Only patients who had completed genetic testing were included in this analysis. Patients were defined as having completed genetic testing if either a diagnostic result was identified through accelerated single-gene testing, or gene panel testing was completed. Age of seizure onset was divided into four categorical groups: <6 months, 6–12 months, 12–24 months, and 24–36 months. Type of first seizure was divided into eight categories: febrile generalized (excluding status, which was defined as a seizure lasting >30 min), febrile focal (excluding status), febrile status (focal or generalized), afebrile focal (excluding status), afebrile generalized (excluding status), afebrile status (focal or generalized), afebrile unclassified, and infantile spasms. Univariate analysis was performed using Fisher’s exact equation and multivariate analysis used a Hosmer-Lemeshow binomial regression model. Statistical advice was from Cunyi Wang of Glasgow University.

**Data availability**

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary material.

**Results**

The mean number of births per year in Scotland for the years 2011 to 2016 inclusive was 56490, making the estimated denominator for this population 169470. During
the 3-year study period, 343 children under the age of 3 years were recruited to this study.

**Phenotypes**

Of 214 patients recruited because of a diagnosis of epilepsy, 101 (47%) presented with focal seizures, 42 (20%) with tonic-clonic seizures, 23 (11%) with myoclonic seizures, 22 (10%) with epileptic spasms, 11 (5%) with absence seizures, eight (4%) with generalized tonic seizures, three (1%) with atonic seizures, and four with unclassified seizures. Ninety-four patients were recruited because of febrile seizures, of whom 45 presented with febrile status, 36 with a cluster of two or more febrile seizures within 24 h, and 13 with recurrent prolonged febrile seizures (>10-min duration). Twenty-three patients were recruited because of an episode of afebrile status epilepticus, and 12 were recruited because of a single cluster of two or more afebrile seizures within a 24-h period. At the time of recruitment, 129 patients did not have a diagnosis of epilepsy, but by the end of the study period, 49 (38%) of these had acquired an epilepsy diagnosis (Table 1). Seventeen different epilepsy syndrome diagnoses were made. The numbers for epilepsy syndrome diagnosis are shown in Table 2. Of 263 patients, 125 (47.5%) remained without an epilepsy syndrome that could be fully classified. Seventy-six (22.1%) patients in the cohort developed therapy-resistant seizures. Finally, 106 (30.1%) had concerns about development expressed at the time of recruitment, and 115 (33.5%) had developmental concerns raised at most recent follow-up.

**Genetic diagnoses**

Three hundred and thirty-three patients completed genetic testing. There was insufficient DNA to complete panel testing for 10 patients. Genetic diagnoses were made for 80 children (24%) (Fig. 1). Supplementary material, part B details all the genetic diagnoses made, along with the phenotypic details for each patient. All but four of the genetic diagnoses were in patients who had a diagnosis of epilepsy by the end of the study period (Table 1). No patient had more than one diagnostic finding. The incidence of single-gene seizure disorders in this population is at least 1 per 2120 live births (47.2/100 000; 95% CI 36.9–57.5). Twenty-six patients had a diagnostic result from accelerated single-gene testing (Sanger and/or MLPA), therefore, these did not undergo panel testing. Of the remaining 307 patients tested on the panel, 52 patients had a diagnostic result. Finally, two patients, following multidisciplinary team discussion, underwent KCNQ2 MLPA testing after a negative panel result and were found to have pathogenic copy number variants. The causative variant was de novo in 34 patients, inherited from an affected parent in 15 patients, inherited from an unaffected parent in nine patients, undetermined in 21 cases, and compound heterozygous in one patient (with POLG-related seizures). Table 2 shows the genetic diagnoses made in relation to phenotype at the end of the study period. High yields from genetic testing were observed in patients classified into the following groups: Dravet syndrome; other developmental and epileptic encephalopathies; self-limited infantile seizures.

The most common single-gene epilepsies were PRRT2 (17 patients), SCN1A (14 patients), KCNQ2 (10 patients) and SLC2A1 (seven patients). Eighty-four per cent (67/80) of genetic diagnoses were in the most frequently-implicated 10 genes. Through interrogating clinical data obtained at presentation and follow-up, we were able to characterize the phenotypic spectrum of several single-gene epilepsies (Table 3 and Fig. 2) and define high yield groups for specific single-gene epilepsies (Table 5). In Table 6 we present univariate and multivariate analysis for associations between presenting features and identification of a single-gene cause. Genetic diagnosis was positively associated with presentation before the age of six months, and with presentation with afebrile focal seizures. These associations remained significant in a multivariate model.

**Gene-associated phenotypes**

**PRRT2: self-limited (familial) infantile seizures**

We identified 17 patients and calculate the minimum incidence as 1 per 9970 live births (10.0/100 000; 95% CI

### Table 1 Diagnoses at recruitment and diagnoses at most recent follow-up

| Diagnosis at recruitment | Diagnosis at most recent follow-up | % Progression to epilepsy |
|--------------------------|-----------------------------------|--------------------------|
| Group                    | n                                 | Epilepsy     | Not epilepsy |                        |
| Recurrent unprovoked seizures (epilepsy) | 214 | 214 | 0 | N/A |
| Afebrile status          | 23 | 13 | 10 | 56.5 |
| Afebrile cluster of seizures within 24 h | 12 | 6 | 6 | 50.0 |
| Febrile status           | 45 | 13 | 32 | 28.9 |
| Febrile cluster of seizures within 24 h | 36 | 12 | 24 | 33.3 |
| Recurrent prolonged febrile seizures (>10 min) | 13 | 5 | 8 | 38.5 |
| Total                    | 343 | 263 | 80 |        |
| Total (%) with a genetic cause identified | 80 (23.3) | 76 (28.9) | 4 (5.0) |        |

N/A = not applicable.
Table 2 Final phenotypes and genetic diagnoses made within each group

| Phenotype at most recent follow up, n | n (%) with a genetic cause identified | Genes implicated (n) |
|---------------------------------------|---------------------------------------|---------------------|
| Epilepsy, 263                         |                                       |                     |
| DEE, 62                               |                                       |                     |
| West syndrome, 27                     | 3/27 (11.1)                           | CDKL5 (2), DEPDCS   |
| Dravet syndrome, 11                   | 1/11 (100)                            | SCN1A (11)          |
| Other DEE, 24                         | 13/24 (54.1)                          | PCDH19 (3), CDKL5 (2), KCNQ2 (2), GABRA1, KCNT1, MECP2, SCN2A, SCN8A, STXBP1 |
| Alper-Huttenlocher syndrome, 1        | 1/1 (100)                             | POLG                |
| Absences with eyelid myoclonia, 1     | 1/1 (100)                             | CHD2                |
| Early onset absence epilepsy, 5       | 0/5                                   |                     |
| Epilepsy with myoclonic-ataxic seizures, 8 | 2/8 (25)                               | STX1B, SLC6A1       |
| Familial focal epilepsy, 1            | 1/1 (100)                             | DEPDC5              |
| Febrile seizures plus, 6              | 0/6                                   |                     |
| Genetic epilepsy with febrile seizures plus, 2 | 1/2                                   | SCN1A               |
| Glut1 deficiency syndrome, 7          | 7/7 (100)                             | SLC2A1 (7)          |
| Myoclonic epilepsy of infancy, 3      | 0/3                                   |                     |
| Panayiotopoulos syndrome, 1           | 0/1                                   |                     |
| Self-limited familial infantile epilepsy, 5 | 5/5 (100)                           | PRRT2 (5)           |
| Self-limited infantile epilepsy, 27   | 11/27 (40.7)                          | PRRT2 (10), KCNQ2   |
| Self-limited familial neonatal seizures, 7 | 7/7 (100)                           | KCNQ2 (5), KCNQ3 (2) |
| Self-limited neonatal seizures, 1     | 1/1 (100)                             | KCNQ2               |
| Unclassified myoclonic epilepsy, 5    | 0/5                                   |                     |
| Unclassified generalized epilepsy, 10 | 1/10 (10)                             | CACNA1A             |
| Unclassified focal epilepsy, 59       | 5/59 (8.5)                            | DEPDC5 (2), KCNA2, KCNQ2, PRRT2 |
| Unclassified focal and generalized epilepsy, 8 | 0/8                                   |                     |
| Unclassified epilepsy, 44             | 6/44 (13.6)                           | SLC6A1 (3), COL4A1, PCDH19, PRRT2 |
| Not epilepsy, 80                      |                                       |                     |
| Febrile seizures only, 64             | 3/64 (4.7)                            | SCN1A (2), KCNA2 (mosaic, 20) |
| Single episode of afebrile status, 10 | 0/10                                  |                     |
| Single cluster of afebrile seizures in 24h, 6 | 1/6 (16.7)                           | CACNA1A             |

DEE = developmental and epileptic encephalopathies.

Figure 1 Genetic results. No case had more than one diagnostic result. Shaded bars represent genes for which there is evidence for precision therapy.
### Table 3 Summary of the clinical findings from the eight most common single-gene epilepsies

| Genetic cause | PRRT2 | SCN1A | KCNQ2 | SLC2A1 |
|---------------|-------|-------|-------|--------|
| Number of patients in this cohort and whether related | 17 (8 female) All unrelated | 14 (5 female) All unrelated | 10 (5 female) All unrelated | 7 (3 female) All unrelated |
| Incidence | 1 per 9970 live births (10.0/100 000; 95% CI 5.26–14.8). | 1 per 12 200 live births (8.26/100 000; 95% CI 3.93–12.6). | 1 per 17 000 live births (5.89/100 000; 95% CI 2.24–9.56). | 1 per 24,300 live births (4.13/100 000; 95% CI 1.07–7.19). |
| Age range at presentation in months (median) | 3–19 (7) | 1.5–19 (6.5) | 0.17–4 (0.24) | 11–18 (12) |
| Most common presentation(s) | Afebrile focal seizures: 71% (12/17) | Febrile seizures: 50% (7/14) | Afebrile focal seizures: 36% (5/14) | Afebrile focal seizures: 70% (7/10) |
| Diagnosis at latest follow-up | Self-limited infantile encephalopathy: 88% (15/17) | Dravet syndrome: 79% (11/14) | Febrile seizures only: 14% (2/14) | Self-limited neonatal epilepsy: 60% (6/10) |
| Follow-up | Status epilepticus: 36% (5/17) | Glut1-deficiency with epilepsy: 20% (2/10) | Genetic epilepsy with febrile seizures plus: 7% (1/14) | Glut1-deficiency with epilepsy: 100% (7/7) |
| Developmental concerns at presentation | 24% (4/17) | 29% (4/14) (29%) | 20% (2/10) | 57% (4/7) |
| Developmental concerns at follow-up | 12% (2/17) | 64% (9/14) | 30% (3/10) | 43% (3/7) |
| Therapy-resistant seizures | None (0/17) | 86% (12/14) | 20% (2/10) | 14% (1/7) |
| Recommended treatment(s) (Table 4) | Carbamazepine | Stiripentol | Carbamazepine | Phenytoin |
| Zygosity | 100% heterozygous (17/17) | 100% heterozygous (14/14) | 100% heterozygous (10/10) | 100% heterozygous (7/7) |
| Inheritance of causative variant | 12% de novo (2/17) | 70% de novo (10/14) | 30% de novo (3/10) | 70% de novo (3/7) |
| | 71% inherited (12/17) | 50% inherited (5/10) | 50% inherited (2/10) | 15% inherited (1/7) |
| | 18% unknown (3/17) | 10% unknown (2/10) | 15% unknown (1/7) | **| |

### Table 3 Summary of the clinical findings from the eight most common single-gene epilepsies

| Genetic cause | CDKL5 | PCDH19 | DEPDC5 | SLC6A1 |
|---------------|-------|--------|--------|--------|
| Number of patients in this cohort and whether related | 4 (3 female) All unrelated | 4 (all female) All unrelated | 4 (2 female) All unrelated | 4 (all female) 3 were siblings |
| Incidence | 1 per 42 400 live births (2.36/100 000; 95% CI 0.805–5.59) | 1 per 20 600 live born females (2.36/100 000; 95% CI 0.81–5.59) | 1 per 24 400 live births (95% CI 1.97–9.15) | N/A |
| Age range at presentation in months (median) | 0.5–6 (1.65) | 5–6 (1.65) | 6–18 (11.5) | 2.5–26 (20) |
| Most common presentation(s) | Infantile spasms: 50% (2/4) Afebrile focal seizures: 50% (2/4) | Afebrile focal seizures: 75% (3/4) | Afibrillary epilepsy: 25% (1/4) | Unclassified focal epilepsy: 25% (1/4) |
| Diagnosis at latest follow-up | CDKL5 developmental and epileptic encephalopathy: 100% (4/4) | PCDH19 related developmental and epileptic encephalopathy: 75% (3/4) | Unclassified epilepsy: 75% (3/4) | Unclassified epilepsy: 75% (3/4) |
| Follow-up | Infantile spasms (West syndrome) 25% (1/4) | Infantile spasms (West syndrome) 25% (1/4) | Infantile spasms (West syndrome) 25% (1/4) | Epilepsy with myoclonic-atactic seizures 25% (1/4) |
| Developmental concerns at presentation | 50% (2/4) | None (0/4) | None (0/4) | 75% (3/4) |
| Developmental concerns at follow-up | 100% (4/4) | 75% (3/4) | 25% (1/4) | 100% (4/4) |
| Therapy-resistant seizures | 100% (4/4) | 50% (2/4) | 50% (2/4) | 50% (2/4) |
| Recommended treatment(s) (Table 4) | Ketogenic diet | Carbamazepine | Clobazam | Sodium valproate |
| Zygosity | 75% heterozygous (3/4) 25% hemizygous (1/4) | 100% heterozygous (4/4) | 100% heterozygous (4/4) | 100% heterozygous (4/4) |
| Inheritance of causative variant | 75% de novo (3/4) | 50% paternally inherited (2/4) | 50% de novo (2/4) | 100% inherited (4/4) |
| | 25% unknown (1/4) | 50% de novo (2/4) | 50% inherited (2/4) | 75% (3/4) |
Two patients had missense variants and 15 patients had frameshift variants, of whom 13 patients had the recurrent frameshift variant (c.649dup, p.Arg217Profs*8). This is the most frequently observed disease-associated PRRT2 variant in the literature (Ebrahimi-Fakhari et al., 2015). The observation that this variant appears over 400 times in the exome aggregation consortium (ExAC) database (Lek et al., 2016) would initially suggest that it is a relatively common population variant. However, the same variant appears just eight times in the genome aggregation consortium (gnomAD) database, which includes the same participants as ExAC but applies a different sequencing methodology (The Broad Institute, 2018). We therefore suspect that the variants seen in ExAC are artefacts that have appeared during the DNA amplification process. In our study we validated all variants through Sanger sequencing and are confident that we have not reported sequencing artefacts. Among 29718 participants in gnomAD for whom there is PRRT2 data, eight were heterozygous for the c.649dup variant. In our study there were 10 patients among 333 tested, making this variant >100 times more common in our study population than in the healthy population.

A clear age pattern of PRRT2-related epilepsy presentation was observed, with peak onset of seizures at 7 months. The phenotype we observed was in keeping with previously published literature on PRRT2-related epilepsy, which describes a self-limited infantile epilepsy which has median age of onset at 6.0 months (Ebrahimi-Fakhari et al., 2015). Outcomes were generally good in our cohort. At most recent follow-up no patients had developed therapy-resistant seizures, and all had been seizure-free for >6 months. Interestingly four patients had developmental concerns highlighted at presentation but only two continued to present developmental concerns at most recent follow-up. This provides a suggestion that with this genetic epilepsy, developmental trajectory may improve along with seizure control as the child gets older. This hypothesis would need to be confirmed by studying more prospective developmental assessments. Effective therapies reported were carbamazepine (n = 7), levetiracetam (n = 5), and sodium valproate (n = 3).

**SCN1A: Dravet syndrome, febrile seizures plus**

We identified 14 patients and calculate the minimum incidence of SCN1A-related seizures as 1 per 12 200 live births (8.26/100 000; 95% CI 3.93–12.6). A spectrum of disease severity was seen. Of 14 patients with SCN1A variants, 11 (79%) were ultimately diagnosed with Dravet syndrome, making the incidence of SCN1A-related Dravet syndrome...
Table 4 Evidence from the literature to support gene-specific treatment approaches

| Gene | Recommendation(s) | n | Study details | P-value | Evidence level | Recommendation grade | Reference |
|------|-------------------|---|---------------|---------|----------------|----------------------|-----------|
| PRRT2 | Consider carbamazepine | 64 | Retrospective uncontrolled clinician-reported subjective treatment response analysis. | NC | III | C | Huang et al. (2015) |
|      |                    | 24 | Retrospective uncontrolled clinician-reported subjective treatment response analysis. | NC | III | C | Ebrahimi-Fakhari et al. (2015) |
| SCN1A | Consider stiripentol | 36 | Placebo-controlled RCT of add-on therapy in Dravet syndrome (number with SCN1A variant not reported). | <0.0001 | IB | A | Chirron et al. (2000) |
|      |                    | 41 | Prospective observational study of long-term efficacy of add-on stiripentol in patients with Dravet syndrome (39 with SCN1A variant). | NC | III | C | Myers et al. (2018) |
|      | Consider cannabidiol | 120 | Multicentre double-blind placebo-controlled RCT of add-on therapy in Dravet syndrome (114 with SCN1A variant). | 0.08 | IB | A | Devinsky et al. (2017) |
|      | Consider fenfluramine | 11 | Retrospective uncontrolled clinician-reported seizure-freedom. | NC | III | C | Ceulemans et al. (2012) |
|      | Consider ketogenic diet | 20 | Retrospective uncontrolled clinician-reported seizure reduction in Dravet syndrome (number with SCN1A variant not reported). | NC | III | C | Caraballo et al. (2005) |
|      | Consider levetiracetam | 28 | Open label uncontrolled trial of add-on lamotrigine in Dravet syndrome (16 with SCN1A variant). | 0.0001 | III | C | Striano et al. (2007) |
|      | Consider topiramate | 1B | Open label uncontrolled trial of add-on topiramate in Dravet syndrome (number with SCN1A variant not reported). | NC | III | C | Coppola et al. (2002) |
|      | Consider sodium valproate | 160 | Retrospective uncontrolled clinician-reported subjective treatment response analysis. | NC | III | C | Brunklaus et al. (2012) |
|      | Avoid carbamazepine | 60 | Retrospective uncontrolled clinician-reported subjective treatment response analysis. | NC | III | C | Brunklaus et al. (2012) |
|      | Avoid lamotrigine | 60 | Retrospective uncontrolled clinician-reported subjective treatment response analysis. | NC | III | C | Brunklaus et al. (2012) |
|      | Consider sodium valproate | 21 | Uncontrolled unblinded trial of add-on lamotrigine in Dravet syndrome (number with SCN1A variant not reported). | NC | III | C | Guerrini et al. (1998) |
| KCNQ2 | Consider carbamazepine | 15 | Retrospective uncontrolled clinician report of seizure-freedom. | NC | III | C | Pisano et al. (2015) |
|      | Consider phenytoin | 15 | Retrospective uncontrolled clinician report of seizure-freedom. | NC | III | C | Pisano et al. (2015) |
| SLC2A1 | Use ketogenic diet | 104 | Retrospective uncontrolled family-reported subjective treatment response analysis. | NC | III | C | Kass et al. (2016) |
| CDKL5 | Consider ketogenic diet | 82 | Retrospective uncontrolled family-reported subjective treatment response analysis. | NC | III | C | Lim et al. (2017) |
| PCDH19 | Consider clobazam | 58 | Retrospective uncontrolled clinician-reported treatment response analysis, 3 months after commencing therapy. | NC | III | C | Lotte et al. (2016) |
| SLC6A1 | Consider sodium valproate | 15 | Retrospective uncontrolled clinician-reported subjective treatment response analysis. | NC | III | C | Johannesen et al. (2018) |
| SCN8A | Consider phenytoin | 0 | Functional study. Single cell patch clamp testing in ND7 cells transfected with the epilepsy-associated variant (I1327V). | NC | III | C | Barker et al. (2016) |
|      | 4 | Retrospective uncontrolled clinician-reported subjective treatment response analysis. | NC | III | C | Boerma et al. (2016) |
| SCN2A (with seizure onset <3 mo of age) | Consider sodium channel blocking (SCB) drugs | 158 | Retrospective clinician-reported seizure-freedom. | $1 \times 10^{-4}$ | III | C | Wolff et al. (2017) |
| POLG | Avoid sodium valproate | 43 | Retrospective clinician-reported hepatotoxicity. | NC | III | C | Angnastou et al. (2016) |
| KCN11 (in patients aged <4 y) | Consider trial of quinidine | 0 | Functional study. Single cell patch clamp testing in Xenopus laevis oocyte cells. | NC | III | C | Milligan et al. (2014) |
|      | 6 | Single centre, inpatient, order randomized, blinded, placebo-controlled trial. | 0.15 | NA | None | Conflicting evidence | Mullen et al. (2018) |

Papers were included if they were either randomized-controlled trials, provided supportive evidence from in vitro functional studies, or analysed a cohort of >10 patients specifically in relation to treatment response. Where multiple treatments were evaluated in the same cohort, evidence is presented in favour of the most efficacious therapy identified. See Supplementary material for a more detailed version of this table.

mo = months; NC = not calculated; y = years.

1 per 15,500 live births. One patient, who had a de novo variant (Patient 90), received a diagnosis of genetic epilepsy with febrile seizures plus (GEFS+). De novo SCN1A variants do not necessarily imply a severe prognosis and have previously been associated with GEFS+ phenotypes (Myers et al. 2017). Two patients had febrile seizures only, one of whom (Patient 5) had an inherited variant from a father with a history of recurrent febrile seizures. For the other (Patient 317), inheritance status could not be determined. Six patients had variants predicted to result in truncation and eight had missense variants, but no genotype-phenotype association was observed in this cohort. One of the patients with a truncating variant (Patient 5) had febrile seizures only. Age at presentation had a similar distribution to that...
of the PRRT2-related seizures, with median onset at 6.5 months. In contrast to patients with PRRT2 variants, those with SCN1A variants were likely to present with febrile seizures and with status epilepticus. Half of the SCN1A patients presented with a febrile seizure and half with an afebrile seizure. The SCN1A phenotype observed in our cohort was in line with the previous literature on this genetic seizure disorder, which reports a tendency for early seizures to be associated with fever, a median initial seizure presentation at 6.0 months and a spectrum of disease severity. While the majority go on to develop a drug-resistant epilepsy and cognitive stagnation or decline (Harkin et al., 2007;
Brunklaus et al. (2012) some, even if their variant has arisen de novo, may have mostly febrile seizures and a good cognitive outcome (Myers et al., 2017). While it is well established that there is a spectrum of SCN1A-related phenotypes, until now the relative proportions of mild versus severe cases has not been established because no study has used a population-based approach to SCN1A testing. Here we show that the majority of SCN1A phenotypes are in fact at the severe end of the spectrum. In our cohort, 11/14 patients were reported to have normal development at the time of presentation. At most recent follow-up five continued to have normal cognitive development, three had mild cognitive concerns and six had moderate cognitive concerns. Eighty-six per cent (12/14) of patients developed therapy-resistant seizures, making SCN1A the most common genetic cause of therapy resistant seizures in this cohort. The most frequently reported effective therapy was stiripentol (n = 4).

KCNQ2: self-limited (familial) neonatal seizures, early infantile developmental and epileptic encephalopathy

We identified 10 patients and calculate the minimum incidence as 1 per 17 000 live births (5.89/10 000; 95% CI 2.24–9.56). Seizures associated with KCNQ2 variants presented significantly earlier than the other single-gene epilepsies in this cohort (median 7 days). Five patients had a frameshift variant, two had a duplication of exons 2–12, two had whole gene deletions, and one had a de novo missense variant. The most severe epilepsy and developmental impairment was observed in the patient with the missense variant. The literature describes two distinct phenotypes associated with KCNQ2 variants: a self-limited familial neonatal seizure phenotype (Biervert et al., 1998; Singh et al., 2003) and a severe neonatal-onset developmental and epileptic encephalopathy (Weckhuysen et al., 2012; Kato et al., 2013; Olson et al., 2017). We also observed these two phenotypes but found that the majority of patients had a mild phenotype. Seven of 10 patients (70%) had self-limited neonatal or infantile-onset seizures, all of whom had normal cognitive development at most recent follow-up. Two patients had KCNQ2 encephalopathy, and one patient had an unclassified drug-resistant focal epilepsy of onset at 3 months and developed mild cognitive impairment.

Previous studies have identified that more severe phenotypes are observed in patients who carry missense variants in KCNQ2 (Weckhuysen et al., 2012; Kato et al., 2013; Olson et al., 2017). In contrast, the majority of familial self-limited cases are associated with truncating variants (Singh et al., 2003). We did not entirely observe this pattern. In our cohort only one patient had a missense variant (Patient 177). This patient had a severe developmental and epileptic encephalopathy, presenting with seizures at 30 days of age. The other patient with a severe developmental and epileptic encephalopathy had a whole gene deletion. We observed a number of patients presenting with focal seizures beyond the neonatal period (one at 3 months and two at 4 months). Post-neonatal presentation with KCNQ2-related seizures has been reported before (Millichap et al., 2017; Zeng et al., 2018). In our cohort early onset of seizures appeared to be associated with better outcomes. All six of those who presented at under 1 month of age had self-limited seizures and normal cognitive development. Inheritance status did not fully correlate with severity of phenotype. One patient with an inherited variant and an extensive family history of self-limited familial neonatal seizures had profound cognitive impairment (Patient 177), suggesting modifying factors were at play. Another patient (Patient 336) with a de novo variant, had self-limited neonatal seizures and a good cognitive outcome.

The most frequently-reported effective therapy was carbamazepine (n = 4), followed by phenobarbitone (n = 3).

SLC2A1: generalized seizures with gait ataxia (Glut1 deficiency)

We identified seven patients and calculate the minimum incidence as 1 per 24 300 live births (4.13/100 000; 95% CI 1.07–7.19). Four patients had truncating variants and three had missense variants. In contrast to all the other genetic causes, these patients were more likely to present with generalized seizures than with focal seizures. Six of seven patients presented with generalized seizures (three tonic-clonic, two myoclonic, one absence). Age at presentation was later than that observed with the other genetic causes, with a median seizure-onset of 12 months. This is slightly later than the median age of 8 months reported by Pong et al. (2012) in their study of 78 patients with SLC2A1-related seizures. The literature on SLC2A1-related phenotypes tends to emphasize the coexistence of early childhood seizures with other clinical features, most notably developmental delay, chorea, dystonia and microcephaly (Di Georgis and Veggiotti, 2013). Nonetheless, the observation that initial seizure presentation in these children is often with absence seizures or myoclonic seizures (Hully et al., 2015) prompted some authors to screen children with early onset absence epilepsy (EOAE) and epilepsy with myoclonic atomic seizures (EMA), for pathogenic variants in the SLC2A1 gene. The conclusions from these studies was that glucose 1 transporter (Glut1) deficiency was associated with a significant minority of these presentations, 12% (Arsov et al., 2012) and 5% (Mullen et al., 2011), respectively. In the seven patients with causative SLC2A1 variants in our cohort only two had myoclonic seizures at any time in their history, and only one has absence seizures. The most frequent presenting seizure type was generalized tonic clonic seizures, an observation supported by the study by Pong et al. (2012), which reported that a generalized tonic clonic seizure was the presenting seizure in 53% of patients with SLC2A1-related seizures.

Beyond the seizures, additional phenotypic features at initial presentation were uncommon. In only two patients was Glut1 deficiency suspected prior to genetic result and only one patient underwent diagnostic lumbar puncture. One patient had a marked four limb dystonia at presentation. All the others were thought to have normal motor
function at the time of their seizure presentation. By the time their genetic result was known, and they were clinically re-reviewed, all six of these had developed a subtle gait ataxia. All seven patients are currently on the ketogenic diet, the established treatment of choice for Glut1 deficiency. Ketogenic diet was perceived to be effective in all cases. At most recent follow-up all seven patients were seizure-free. Four had normal cognition and three had mild cognitive concerns. Long-term follow-up of this cohort and comparison with historical cohorts may help determine whether early instigation of the ketogenic diet is associated with improved outcomes.

**Therapy-response and precision therapy:**

Seventy-six patients developed therapy resistant seizures, 36 of whom (47%) had a single-gene cause identified. Therapy-resistance was not observed in any patients with PRRT2 variants, and was seen in only 2/10 patients with KCNQ2 variants. Just one patient with SLC2A1-related seizures developed therapy-resistance. The good seizure outcome observed in Glut1 deficiency may be related to early establishment of the ketogenic diet. The only single-gene epilepsies for which more than two patients developed therapy-resistance were SCN1A (12 patients), CDKL5 (four patients), and PCDH19 (four patients). Between them, these three genes accounted for 20/76 (26%) of all therapy-resistant cases in this cohort. Literature review identified evidence to support specific treatment approaches for 64 (80%) of our 80 children with genetic diagnoses (Table 4).

**Discussion**

In this study we have used a whole population prospective cohort design to determine the incidence of the more common single-gene epilepsies of early childhood. Recruitment to our cohort was consistent across all 24 centres, which represent all health facilities where young children are expected to present with seizures. Patient ascertainment and exclusion of duplicate reporting were well managed in the recruitment process by cross-referencing within clinical departments, attending physicians, specialist epilepsy nurses, EEG departments and the central genetic laboratory.

The panel of 104 established epilepsy-associated genes was designed to capture all the more commonly-implicated genes, with a specific focus on those for which precision treatment approaches exist. As some genetic epilepsies initially present with prolonged febrile seizures (Brunklaus et al., 2012; Higurashi et al., 2013; Ebrahimi-Fakhari et al., 2013) children with status, clusters of febrile seizures, and recurrent prolonged febrile seizures were included.

The approach to determination of diagnostic genetic results involved comprehensive review of genetic and phenotype data within a multidisciplinary environment. Genetic results were reported in accordance with UK best practice guidelines (Association for Clinical Genetic Science, 2017). Where DNA samples and/or phenotype details from other family members were considered relevant to variant interpretation these were requested. We agree with Anderson and Lassmann (2018) that variants cannot be considered in isolation from phenotypes and relevant variant interpretation requires a multidisciplinary approach.

The incidence of epilepsy in children under 36 months of age has previously been estimated in a US population-based cohort as 1 per 613 live births (Wirrell et al., 2012). Our cohort represents 1 per 495 live births in Scotland. Direct comparison between these cohorts is not appropriate as our study included children presenting with certain febrile seizure presentations and excluded those with established non-genetic causes. In our cohort, 163 patients presented with recurrent afebrile seizures before the age of 12 months, giving an estimated incidence of infantile-onset epilepsy of 1 per 1041 live births (96.0/100 000; 95% CI 81.8–112.0). This is comparable to the figure of 1 per 1240 live births derived from a 20-year population-based cohort in Helsinki (patients with structural-metabolic causes removed) (Gaily et al., 2016) and the figure of 1 per 1220 from a North London cohort (Eltze et al., 2013).

It is established that single-gene aetiology can be identified in a substantial proportion of patients presenting with early-childhood onset epilepsy. Berg et al. (2017) carried out a prospective study in which they aimed to determine aetiology in all patients with epilepsy presenting before the age of 3 years, regardless of severity. Participants were recruited from 17 epilepsy centres in the US (Berg et al., 2017). Their study was not population-based and used a variety of testing methods that were not consistent between centres. They reported a diagnostic yield of 29.2% for those tested on epilepsy gene panels, and 27.8% for those tested by whole-exome sequencing. These yields are slightly higher than in our study. In Berg et al.’s study the majority of patients (266/446) without determined aetiology did not undergo any form of genetic testing so those results are likely to have been affected by a degree of ascertainment bias.

In comparison with some recently published studies of genetic testing in epilepsy (Heyne et al., 2018; Lindy et al., 2018) ours includes a smaller cohort of patients. The strength of the present study relates to case ascertainment. The broad inclusion criteria and proactive recruitment strategy applied allowed a better understanding of both the full phenotypic spectrum and the incidence of the single-gene epilepsies in childhood. For the most frequently encountered single-gene epilepsies in this cohort—namely, PRRT2, SCN1A, KCNQ2 and SLC2A1—we observed phenotypic spectra that were largely in keeping with the literature published previously. However, we demonstrated that these are more common than has been previously described. Previous reports have estimated the incidence of SCN1A-related Dravet syndrome in
California (1 per 20 900 live births) (Wu et al., 2015) and in Denmark (1 per 22 000 live births) (Bayat et al., 2015) but neither study used prospective case ascertainment strategies. Our study estimates the incidence of SCN1A-related Dravet syndrome to be 1 per 15 500 live births (11 patients with SCN1A-related Dravet syndrome). The incidence of Glut1 deficiency has previously been estimated as 1 per 90 000 live births in Queensland (Coman et al., 2006) and 1 per 83 000 live births in Denmark (Larsen et al., 2015) compared with 1 per 24 300 live births in this study. These figures are not likely to represent a Scottish population-specific phenomenon since the majority of cases of Dravet syndrome and Glut1 deficiency are caused by de novo variants. Estimated incidences for PRRT2, CDKL5, DEPDC5, and PCDH19-related epilepsies are provided here for the first time.

Previous studies investigating the yield of NGS in epilepsy have found that the majority of diagnoses are concentrated in a small number of recurrently-implicated genes. Lindy et al. reported the results of testing >8500 patients using a 70-gene epilepsy panel. They quoted a yield of 15.4% (Lindy et al., 2018). As with our study >80% of their diagnoses were in the most frequently-implicated seven genes. Six of our seven most frequently-implicated genes were among their seven most frequently-implicated (DEPDC5 was not included in their panel). We identified a substantially higher rate of PRRT2 variants in this cohort than have been reported in previous studies (Helbig et al., 2016; Trump et al., 2016; Lindy et al., 2018). This is likely to reflect our inclusion of self-limited and pharmaco-responsive epilepsies that would not have previously been considered candidates for high throughput genetic testing.

For a number of reasons this study is likely to have underestimated the incidence of single-gene epilepsies in this group, so our incidence figures are best considered as minimum incidences. Some genes associated with epilepsy are not on our panel, and for some genes (e.g. SCN1A and KCNQ2) we were able to offer more comprehensive testing than for others through MLPA. Chromosomal microarray for deletions and duplications was not part of our routine testing strategy due to the low reported yield in this group, low penetrance of many epilepsy-associated variants, and absence of evidence that identification of chromosomal lesions supports a precision medicine approach. Though the inclusion criteria for our study were broad, we are likely to have missed some patients with very mild phenotypes—e.g. recurrent simple febrile seizures—who did not meet eligibility criteria. The identical twin of Patient 334 had the same PRRT2 variant as her sister but was not eligible for inclusion since all her seizures were febrile and <10 min duration. Similarly, SCN1A-related disease can present with simple febrile seizures only (Escayg et al., 2000). A complex febrile seizure has been defined by some authors as a febrile seizure that has any one of the following elements: focal features, duration >15 min, recurring more than once in 24 h, or associated with postictal palsy or previous neurological deficits (Capovilla et al., 2009). Our criteria did not include children with febrile seizures with focal features lasting <10 min or those with a single febrile seizure lasting between 10 and 30 min as duration and frequency of febrile seizure were considered more reliable clinical predictors of SCN1A, PCDH19 and PRRT2 variants.

We are likely to have underestimated the incidence of SLC2A1-related disease as not all patients with Glut1 deficiency will present with seizures in the first 3 years of life. The same is true for several other genetic epilepsies and neurodevelopmental disorders, including CDKL5, DEPDC5, POLG, SCN2A, MECP2, KCNT1 and GABRA1.

According to our protocol patients were not recruited to the study if they had an aetiology identified either prior to or at initial presentation with seizures. As a result, patients are likely to have not been recruited if they had acute neuroimaging findings that were deemed to explain their epilepsy, even if such findings may indeed have an underlying genetic basis. The most notable example of this would be tuberous sclerosis, caused by TSC1/TSC2 variants, where neuroimaging findings are often highly typical for this genetic disorder and the diagnosis may be known prior to onset of seizures. Patients with other genetically determined developmental brain malformations may also not have been recruited. Neonates with symptomatic seizures secondary to hypoxic ischaemic encephalopathy (HIE) at birth were not recruited. Rarely, genetic metabolic disorders such as pyridoxine dependency, sulphite oxidase deficiency, or molybdenum co-factor deficiency may mimic pyridoxine dependency (Baxter, 1999). We would expect these children to continue to have seizures beyond the neonatal period and to be seen within one of Scotland’s tertiary child neurology centres. Finally, we only tested DNA samples derived from blood and it has been shown that some genetic epilepsies are due to somatic variants (Nellist et al., 2015).

Evidence from randomized controlled trials (RCTs), open label trials, retrospective case series, and from in vitro functional studies, informs clinicians’ treatment choice when they make a diagnosis of a single-gene epilepsy. Such evidence exists for SCN1A, PRRT2, KCNQ2, SLC2A1, PCDH19, POLG, SCN2A, and SCN8A (Table 4). On this basis we estimate that 64/80 (80%) of the single-gene diagnoses made in this study had potential treatment implications. In the case of Glut1 deficiency, early diagnosis and implementation of the ketogenic diet may have an impact on developmental and motor comorbidity as well as seizure control (Kass et al., 2016). In SCN1A-related epilepsy, duration of use of contraindicated sodium-channel blocking medication is associated with adverse developmental outcome (de Lange et al., 2018). Additional benefits of early genetic diagnosis in epilepsy include providing information for genetic counselling (Krabbenborg et al., 2016), giving answers for affected families (Brunklaus et al., 2013; Sawyer et al., 2016; Wynn et al., 2018), and avoidance of
additional costly and invasive investigations. Recent economic analyses have demonstrated that the application of early high throughput genetic testing could save $5236 Australian dollars (Palmer et al., 2018), or $7047 US dollars (Howell et al., 2018) per diagnosis when compared with investigation programs that involved extensive imaging and metabolic testing prior to genetic testing.

Evidence in support of precision therapy in epilepsy varies in level and nature. In 2019, the majority of truly medically ‘actionable’ genetic diagnoses in epilepsy relate to inherited disorders of metabolism such as Glut1 deficiency, and pyridoxine dependency (Peng et al., 2019). Questions remain unanswered in relation to targeted treatment of other genetic causes of epilepsy. Much of the evidence that we have presented to support gene-specific therapy approaches in Table 4 is at level III. Non-RCT evidence is compromised by the absence of control groups, variability in timing and objectivity of response analysis, and inconsistent reporting of concomitant drug use. As exemplified by KCNT1-related seizures, evidence can be conflicting. Here, despite positive anecdotal reports of benefit from quinidine (Bearden et al., 2014; Fukuoka et al., 2017; Abdelnour et al., 2018) and supportive in vitro functional studies (Milligan et al., 2014) a small randomized-controlled crossover trial demonstrated no significant benefit in adult patients with KCNT1-related frontal lobe epilepsy (Mullen et al., 2018). Nevertheless, in reality, many clinicians if faced with a child with unremitting seizures associated with a KCNT1 variant may be inclined to at least give a trial of quinidine—a drug that they would be unlikely to use for seizures in any other scenario. The recommendation grade for specific therapy in most of the genetic epilepsies is grade C. Nonetheless it is important to note that such evidence is the basis of therapy choice in almost all epilepsy syndromes and may provide a key lead in to definitive trials, as has been the case with fenfluramine in Dravet syndrome (NIH US National Library of Medicine, 2019). Findings from RCTs must also be interpreted in context. In Dravet syndrome cannabidiol demonstrates efficacy (Devinsky et al., 2017); however, there is no biological reason why cannabidiol should be specifically effective in this condition because it does not appear to act on sodium channels or GABA receptors (Devinsky et al., 2014). Cannabidiol also has efficacy in Lennox Gastaut syndrome (French et al., 2017; Devinsky et al., 2018), an epilepsy with varied aetiologies. Several other broadly-acting anti-epileptic therapies including levetiracetam, topiramate, and the ketogenic diet have performed just as well as cannabidiol in open label uncontrolled studies of Dravet syndrome, but as they have not been tested in RCT format they are considered less evidence-based (Coppola et al., 2002; Caraballo et al., 2005; Striano et al., 2007; Devinsky et al., 2018). In contrast the ketogenic diet is regarded as the gold standard therapy in Glut1 deficiency in the absence of any RCT data. Obtaining good quality evidence for gene-specific treatment approaches in epilepsy is perceived as a challenge, since many of these disorders are exceedingly rare. To this end, defining the incidence of the more common difficult to treat genetic epilepsies of childhood is an important step. Orphan medicinal products have been developed and licensed for many rarer conditions than the genetic epilepsies (European Joint Programme Rare Diseases, 2019). Gene therapy approaches, which may provide definitive precision therapy, are being trialled in rodent and non-human primate models of human genetic epilepsies (Berkovic et al., 2015). In this study, 36/80 patients with single-gene epilepsy had therapy-resistant seizures. Of these 20 (56%) were associated with just three genes, SCN1A, CDKL5, and PCDH19. For maximum benefit, these are the genetic epilepsies that should be prioritized in the development of precision therapy.

**Study limitations**

Although we aimed to include all children with epilepsy presenting in Scotland under the age of 3 years, it is possible that some patients were unreported and not included. Therefore, all incidences reported in this study should be viewed as minimum estimates.

Children with epilepsy due to other identifiable causes such as hypoxic ischaemic encephalopathy, meningitis, metabolic disorders, etc. were excluded. However, some of these patients may have had genetic ‘mimics’ of acquired causes, genetic causes of structural brain abnormalities, or compound genetic-acquired aetiologies. Their exclusion may have reduced the yield of genetic diagnoses in this study.

The health economics of genetic testing in this group of children were not examined, but it is possible that early identification of a genetic diagnosis would save other costly investigations.

This cohort is being followed up to determine whether there is a positive impact of early genetic diagnosis and treatment on a child’s neurodevelopment and comorbidities. However, this study will take several years to report its conclusions.

**Conclusions**

Single-gene epilepsies are more common than previously reported, with a collective minimum incidence of about 1 per 2000 live births. Many of the cases identified in this study are dominant genetic epilepsies due to de novo mutations. Therefore these minimum incidence figures are applicable to other populations and are not specific for Scotland.

Our data suggest that genetic testing should be a primary investigation for epilepsies presenting in early childhood. The nature of genetic testing will depend upon available...
resources. Eighty per cent of genetic diagnoses in this group relate to eight genes, with other genetic aetiologies likely to be individually extremely rare. A clinically relevant and economically efficient testing paradigm would be to analyse a small panel of genes and if this is unrevealing move to a larger platform such as clinical exome, whole exome or whole genome.

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Competing interests
The authors report no competing interests.

Supplementary material
Supplementary material is available at Brain online.

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