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Familial neonatal seizures in 36 families: clinical and genetic features predict outcome

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Familial neonatal seizures in 36 families: clinical and genetic features predict outcome

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For Review Only

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For Review Only

Abstract

Objective: We evaluated seizure outcome in a large cohort of familial neonatal seizures and examined phenotypic overlap with different molecular lesions.

Methods: Detailed clinical data were collected from 36 families comprising two or more individuals with neonatal seizures. The seizure course and occurrence of seizures later in life were analyzed. Families were screened for *KCNQ2*, *KCNQ3*, *SCN2A* and *PRRT2* mutations and linkage studies were performed in mutation-negative families to exclude known loci.

Results: Thirty-three families fulfilled clinical criteria for benign familial neonatal epilepsy (BFNE); 27 of these families had *KCNQ2* mutations, one had a *KCNQ3* mutation and two had *SCN2A* mutations. Seizures persisting after age 6 months were reported in 31% of individuals with *KCNQ2* mutations; later seizures were associated with frequent neonatal seizures. Linkage mapping in two mutation-negative BFNE families excluded the known loci. The three remaining families did not fulfil criteria of BFNE due to developmental delay or intellectual disability; a molecular lesion was identified in two; the other family remains unsolved.

Significance: Most families in our cohort of familial neonatal seizures fulfil criteria for BFNE; the molecular cause was identified in 91%. Most had *KCNQ2* mutations but two families had *SCN2A* mutations, which are normally associated with a mixed picture of neonatal and infantile onset seizures. Seizures later in life are more common in BFNE than previously reported and are associated with a greater number of seizures in the neonatal period. Linkage studies in two families excluded known loci, suggesting a further gene is involved in BFNE.

Key words: Epilepsy; Genetics; Ion channels; Neonatal seizures; Clinical neurology

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Introduction

Familial neonatal seizures comprise a small but important subset of seizures seen in the newborn period [1; 2]. While neonatal seizures often suggest a serious brain injury, a family history of neonatal seizures indicates a more benign course is likely. Two autosomal dominant epilepsy syndromes may present with neonatal seizures – Benign Familial Neonatal Epilepsy (BFNE, OMIM #121200) and Benign Familial Neonatal-Infantile Epilepsy (BFNIE, OMIM #607745).

BFNE is characterized by neonatal onset of seizures, typically on the second or third day of life, that resolve by 6 months of age. Development is usually normal and febrile or afebrile seizures later in life are reported in approximately 15% of cases [3; 4].

Mutations in two potassium channel subunit genes are associated with BFNE. *KCNQ2* mutations are the most common with more than 80 different mutations described [5], while *KCNQ3* mutations are rare [6-8]. A single family with BFNE and a chromosome 5 inversion has been described [9].

Neonatal seizures are also a feature of BFNIE, which is associated with mutations in the sodium channel subunit gene, *SCN2A* [10]. The key clinical feature of BFNIE is that family members vary in their age of seizure onset from the neonatal to the infantile period, with the mean age being 11 weeks.

Here we examine the clinical and molecular features of 36 familial neonatal seizure families and analyze the clinical overlap of syndromes caused by *KCNQ2*/*KCNQ3* and *SCN2A* mutations. We evaluate the frequency and nature of seizures that occur later in life in affected individuals.

For Review Only

Materials and methods

Patient ascertainment

Families with more than one member affected with neonatal-onset seizures were identified from the Epilepsy Research Centre's database. Families were referred from Australia, New Zealand, Israel, the UK and Canada over a 20-year period. BFNE was operationally defined as families where seizures commenced in the neonatal period in at least 75% of affected family members, with normal developmental outcome. We excluded families with a mixed neonatal and infantile onset picture consistent with BFNIE.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Human Research Ethics Committees of Austin Health, the Royal Children's Hospital Melbourne and the Women's and Children's Health Network, Australia. Informed consent was obtained from all participating individuals and parents/guardians in the case of minors.

Of the 36 families reported here, the clinical and molecular findings of eight families have been previously described [12-17] although additional affected children have subsequently been born. The molecular findings in an additional eight families have also been briefly reported [18].

Mutation screening

Patients were analysed for mutations in *KCNQ2*, *KCNQ3* and *SCN2A* by single-stranded conformation polymorphism analysis (SSCA) or by direct sequencing. Direct sequencing was done in all cases where a mutation was not detected by SSCA. Family members and anonymous blood bank controls were analysed for mutations by either SSCA, direct sequencing, restriction enzyme (RE) digestion or high-resolution melting (HRM) analysis.

For Review Only

Mutation negative families were also analysed for mutations in *PRRT2,* the gene for most cases of benign familial infantile epilepsy [19].

Multiplex ligation-dependent probe amplification (MLPA)

Patients without mutations detected by direct sequencing were analysed for exonic deletions and duplications in *KCNQ2* and *KCNQ3* by MLPA using the SALSA MLPA kits P166 lot#0606 and P197 lot#1206 respectively. MLPA results were analyzed using GeneMarker (SoftGenetics).

Breakpoint PCR

Long-range PCR for the identification of deletion breakpoints was carried out as previously described[14].

Single nucleotide polymorphism (SNP) genotyping

SNPs within *KCNQ2* with a minor allele frequency of greater than 10% in the European population that also altered a restriction site were genotyped to determine haplotypes and to localize deletion breakpoints. SNPs were identified from dbSNP (http://www.ncbi.nlm.nih.gov/snp). Suitable restriction enzymes were identified using REBASE® (http://rebase.neb.com).

Linkage analysis

Families without detected pathogenic sequence variants were analysed for linkage to *KCNQ2*, *KCNQ3*, *SCN2A* and the breakpoints of the chromosome 5 inversion. Microsatellite markers (see supplementary data) were genotyped by denaturing gel electrophoresis using the GelScan 3000 (Corbett Research) or capillary electrophoresis using the ABI 3130 Genetic Analyzer.

Comparative Genome Hybridization (CGH)

For Review Only

Hybridization and scanning of arrays for CGH were carried out by Roche-Nimblegen using arrays as described in the Supplemental methods. Data from these arrays were analyzed using SignalMap™ (Nimblegen).

Clinical data and outcome assessment

Clinical information was obtained where possible by a validated seizure questionnaire [11] from subjects and parents and by review of medical records. Exhaustive attempts were made to get data on all affected relatives with emphasis on long outcome with respect to seizures. Seizure frequency in the neonatal period was estimated based on clinical notes and recall of parents. Cases were assigned to those with 20 neonatal seizures or less, or more than 20 neonatal seizures. This is an arbitrary boundary and it is acknowledged that these estimates are inexact and in some cases no determination could be made.

Formal assessment of developmental outcome was not attempted due to the cross-sectional nature of family studies, but cases of intellectual disability were identified based on treating physician notes.

For Review Only

Results

We identified 36 families with familial neonatal seizures and putative autosomal dominant inheritance, (figure 1). Thirty-three families fulfilled our criteria for BFNE. The remaining three families were excluded from the diagnosis of BFNE due to the presence of intellectual disability or developmental delay.

A molecular lesion was identified in 32 (89%) of the 36 families (table 1, table 2, figure 1), including in 30 of the 33 families classified as BFNE (91%). Twenty-seven (82%) BFNE families had *KCNQ2* mutations; these comprised 16 substitutions, five insertions/deletions, four unique exonic deletions (one seen in two separate families) and one exonic duplication[14]. One BFNE family had a missense mutation in *KCNQ3* (family 29) and two families had *SCN2A* mutations (families 30 and 31).

Of the three families not fulfilling our criteria for BFNE, family 8 had a missense mutation of *KCNQ2* [17] while family 32 had a duplication of chromosome 2q24.3 [16]. None of the mutations were detected in at least 50 control samples.

BFNE: Neonatal seizure characteristics in KCNQ2 mutation-positive subjects

The 27 BFNE families with *KCNQ2* mutations comprised 130 subjects with confirmed mutations. One hundred of the mutation-positive individuals (77%) had seizures in the neonatal or infantile period, including nine subjects reported to have had seizures as babies, but specific details regarding timing were not available. In 22 subjects (17%) lack of seizures in the neonatal or infantile period was confirmed by questioning the parents. In the remaining eight individuals affected status was uncertain as witness accounts were not available.

The median age of seizure onset was 3 days (exact onset day known in 87 subjects): 82 had onset in the neonatal period (range 1-28 days) and five babies had onset between 5 weeks and

For Review Only

4 months. Two of the babies with infantile onset were born prematurely: individual 22-IV-3, born at 32 weeks gestation, had seizures beginning at 35 days of age (corrected age of seizure onset 39 weeks), and individual 7-IV-2, born at 36 weeks gestation, had seizures commencing at 4 months (corrected age 3 months).

Seizure types based on clinical description were focal or bilateral clonic or tonic seizures and were often associated with apnea, head or eye deviation or a glazed stare. Neonatal EEG reports were available from 41 individuals. In five cases seizures were recorded and these arose from the central regions in three, and varied in location from seizure to seizure in the other two. Interictal focal epileptiform activity was seen in an additional 11 subjects, which was multifocal in nine and unifocal in two (right frontal and left temporal). Twenty-five interictal recordings were normal or had minor non-epileptiform features.

Seizure frequency in individuals varied from two to estimates of hundreds in 13 (13%). Seizures ceased by 6 months in the majority of cases, although three individuals had their stereotypic seizures until 8-15 months, and the precise age of the last seizure was unavailable for 20% of cases.

BFNE: Later seizures in KCNQ2 mutation-positive subjects

Forty of the 130 (31%) *KCNQ2*-mutation positive individuals from BFNE families had seizure types other than neonatal or infantile seizures (supplemental table e-1). Three patterns of later seizures were identified (figure 2): 1) Simple febrile seizures in late infancy or early childhood (n=18); 2) Seizures in childhood (n=14); 3) Seizures predominantly in teens or adulthood sometimes occurring as sporadic seizures or in clusters over a few months or years (n=19). Seven of the forty patients showed two patterns, and two individuals demonstrated all three patterns. Six individuals with later seizures did not have preceding neonatal or infantile seizures; four of these had their first seizure in adolescence or adulthood (figure 2).

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In the majority of cases adequate data were unavailable to accurately determine localization of focal seizures or diagnose specific epilepsy syndromes. Thirteen individuals had focal-onset seizures, including four with a history suggestive of benign epilepsy with centrotemporal spikes (BECTS), although a diagnostic EEG was only available for one. Seven individuals had tonic-clonic seizures (TCS) that were regarded as generalized but the seizure onsets were rarely witnessed or descriptions were not available; four of these individuals also had febrile seizures.

Those with a larger number of neonatal seizures had a greater likelihood of later seizures. Later seizures were observed in 7/49 individuals (14%) with <20 neonatal seizures compared to 18/30 individuals (60%) who had >20 neonatal seizures, (OR=9, 95% CI: 3.05 to 26.59, p=0.0001).

BFNE: Families with mutations of other genes (figure 1b)

Family 29 had a missense mutation in *KCNQ3*; nine affected individuals had neonatal seizures ceasing by 3 months of age; all were cognitively normal.

Two families were initially classified as having BFNE, but *SCN2A* mutations were identified. Family 30 contains five affected members although only three were initially available: two siblings had seizures commencing on day 3, while their father was said to have had febrile seizures at 3 months. Later information revealed the father's seizures occurred without fever and a fourth family member was born with seizures commencing at 3 months. Age of onset was not available for the fifth family member. Family 31 had six members with verified neonatal seizures (day 2-3), one with confirmed infantile onset (12 weeks) and one individual who did not carry the *SCN2A* mutation, but had febrile and afebrile seizures from 18-36 months.

Benign familial neonatal epilepsy: Mutation-negative families (figure 1c)

For Review Only

No *KCNQ2*, *KCNQ3*, *SCN2A* or *PRRT2* mutations were detected in three BFNE families. Family 33 comprised 11 affected family members with normal development. Six had seizure onset in the first week of life and one at 2 months, while the remainder were unknown. Seizures ceased by 12 weeks except in one individual who was believed to have seizures throughout childhood.

Five individuals in family 34, related through common grandparents, had neonatal seizures commencing on days 1-5 and ceasing by 6 months. Cognitive outcome was normal. There was no history of seizures in the parents of the affected children as determined by close questioning of the grandmother.

Family 35 contained four affected siblings with focal seizures commencing on day 1-3 and ceasing by 4 months. EEGs showed multifocal epileptiform activity in two, a right inferior frontal seizure was recorded in one case and the fourth had a normal EEG.

Microsatellite marker analysis excluded linkage to the relevant regions for *SCN2A* and *KCNQ3* in all three families. Linkage to *KCNQ2* was excluded for families 34 and 35 but was not excluded for family 33; however, chromosome 20 specific CGH revealed no abnormalities. Linkage to both breakpoints of the chromosome 5 inversion was also excluded in families 33 and 34. Linkage to the p-arm breakpoint could not be excluded in family 35 but chromosome 5 specific CGH revealed no abnormalities in the region. Whole-genome CGH revealed no abnormalities in any of the three families.

Non-BFNE families

In three families developmental delay or intellectual disability were seen in some family members.

For Review Only

A *KCNQ2* missense mutation was identified in the proband of family 8 (patient 1 in ref 17) who was severely affected with neonatal epileptic encephalopathy. She inherited the mutation from her mildly affected father who was mosaic for the mutation.

A 1.57Mb duplication on chromosome 2 incorporating *SCN2A*, part of *SCN1A*, and seven other genes was identified in family 32 as previously reported [16]; similar duplications in this region associated with neonatal seizures and intellectual disability have subsequently been reported [20; 21]. Four family members had neonatal seizures, which ceased between 5 and 19 months. All affected individuals had learning difficulties or mild-moderate intellectual disability.

In family 36 two sisters and their mother had neonatal seizures, with both sisters also experiencing mild developmental delay. No point mutations or intragenic deletions or duplications of *KCNQ2*, *KCNQ3* or *SCN2A* have been identified and whole genome CGH-array was normal.

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Discussion

Of 36 families with familial neonatal seizures, 33 fulfilled criteria for BFNE. The molecular lesion underlying the seizure disorder was identified in 91% of BFNE families, with *KCNQ2* being the most common gene. This is in agreement with recent reports of small cohorts of BFNE [7; 8]. In 2003 Singh *et al* found *KCNQ2* mutations in 17 of 30 families (57%) using SSCP [22], however sequencing was not performed, and families were not screened for mutations in *SCN2A* or for microdeletions and duplications in *KCNQ2*.

Two families initially regarded as BFNE were found to have *SCN2A* mutations, the main cause of BFNIE. In this disorder seizure onset is either in the infantile or neonatal periods, with the former predominating [10]. This highlights the challenge of clinico-molecular correlation of these disorders, especially in small families, which has previously been observed [7; 23; 24]. Family 31 is the first *SCN2A* mutation positive family reported with neonatal seizures being the predominant phenotype. Arguments for basing the classification of these disorders on the molecular lesion have been presented elsewhere [25].

Three BFNE families did not have *KCNQ2*, *KCNQ3* or *SCN2A* mutations. The clinical presentation of these three families was indistinguishable from the mutation positive families. Linkage studies in families 34 and 35 excluded known genes associated with familial neonatal or infantile seizures and provide evidence for a third BFNE locus.

Epileptology of KCNQ2-related BFNE

Consistent with the literature, the age of seizure onset in our *KCNQ2* mutation-positive subjects was remarkably tightly clustered [4]. Rare outliers with seizure onset after the first 4 weeks of life have been described; delayed onset is sometimes attributed to prematurity [3; 22]. In our series 5% (5/100) of individuals had onset after 4 weeks of age, which in most cases cannot be explained by premature delivery.

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Seizure remission in BFNE occurs around 4-6 months of age irrespective of treatment. Rare patients, including three in this cohort, continue to have the stereotyped seizures into the second year of life [26; 27]. While this occurs infrequently, it is important for clinicians and families to be aware that patients may require treatment beyond 6-12 months of age.

Penetrance of the *KCNQ2* mutations for the phenotype of neonatal or infantile seizures was approximately 77%; 22 individuals with mutations did not have neonatal seizures although seven did experience seizures later in life, and the affected status of eight individuals carrying mutations was uncertain. This figure is similar to a previous estimated penetrance of 85% [4]. Both estimates are likely somewhat inflated as not all unaffected family members were genotyped.

Epileptic encephalopathy with neonatal seizures resulting from *KCNQ2* mutations is now well recognized and is mainly due to *de novo* mutations [17]. However, families including individuals with *KCNQ2* encephalopathy and others with the benign outcome typical of BFNE have been reported [8; 28-30]. Three of our families contained members with poor outcome, but only one had a *KCNQ2* mutation. In this family the father, who had normal development, had somatic mosaicism and this reduced mutation load may explain the difference in outcome between father and daughter [17]. This mechanism does not explain other families reported in the literature.

Later seizures in KCNQ2-related BFNE

Seizures occurring beyond the first year of life that are either distinct in their clinical manifestation or occur after a prolonged seizure-free period are well known to occur in BFNE families at a rate higher than expected in the general population [3; 4]. Later seizures were seen in 31% of *KCNQ2* positive individuals in our cohort. Pure febrile seizures occurred in 6% of cases, a figure comparable to the 5% previous reported [4; 30] and slightly higher than

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the population frequency of approximately 2-4% [31]. The frequency of later afebrile seizures in BFNE has been estimated at 11-18% [4; 22]. We found 25% of our cases with *KCNQ2* mutations had afebrile seizures after 12 months of age, some with preceding febrile seizures. Even this figure may be an underestimate as the duration of follow-up was short for some patients.

Later seizure types reported in *KCNQ2*-positive families are most commonly described as febrile seizures, afebrile TCS, nocturnal convulsions, focal seizures or unclassified seizures [7; 22; 32; 33]. In most of these reports diagnosis of later recurrences into recognized epilepsy syndromes was not made but, where adequate data was available, focal seizures were the most common seizure type.

While we found it difficult to classify specific epilepsy syndromes in our cohort, we did observe that seizures could be grouped into three patterns: 1) febrile seizures (single or multiple) in late infancy or early childhood, 2) seizures in childhood which were predominantly focal with some generalized seizures 3) sporadic single seizures or clusters of seizures predominantly in teen years or adulthood. These patterns can also be recognized in previous reports of BFNE families with later seizures [7; 22; 32; 33], with the sporadic seizures through adolescence and adulthood being particularly notable. There appears to be considerable phenotypic heterogeneity in the later seizures in these families, even though we could usually not precisely classify the epilepsy syndromes.

The higher than expected frequency of later seizures in BFNE families raises the possibility that mutations in *KCNQ2* contribute to the etiology of other epilepsies. The role of *KCNQ2* and *KCNQ3* in the common idiopathic epilepsy syndromes remains unresolved [34; 35], and there is some evidence that mutations of *KCNQ2* or *KCNQ3* may play a role in the development of BECTS [35-37].

For Review Only

We found that individuals with a greater number of seizures in the neonatal period were more likely to experience seizures later in life compared with individuals who experienced fewer neonatal seizures. However, this was a retrospective study so data regarding the number of seizures was inexact and recall bias may have occurred. If true, this finding may implicate an acquired seizure susceptibility resulting from an increased number of seizures, or perhaps genetic modifiers leading to increased seizures in the neonatal period and also later in life.

Abbreviations

BECTS: Benign epilepsy with centrotemporal spikes; BFNE: Benign familial neonatal epilepsy; BFNIE: Benign familial neonatal-infantile epilepsy; CGH: Comparative genome hybridisation; EEG: Electroencephalogram; FNS: Familial neonatal seizures; FS: Febrile seizures; GEFS+: Genetic epilepsy with febrile seizures plus; HRM: High resolution melting-curve; MLPA: Multiplex ligation-dependent probe amplification; PCR: Polymerase chain reaction; SNP: single nucleotide polymorphism; SSCA: Single-stranded conformation polymorphism analysis; TCS: Tonic-clonic seizure.

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Disclosure of Conflicts of Interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1: Summary of clinical syndromes and molecular findings in 36 families with familial neonatal seizures

Clinical syndrome	**Molecular lesion**	**Number of families**
Benign familial neonatal epilepsy	*KCNQ2*	27
	KCNQ3	1
	SCN2A	2
	Unknown	3
Familial neonatal epilepsy & epileptic encephalopathy or other neurological features	*KCNQ2*	1
	Chr 2 dup	1
	Unknown	1

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Table 2: Summary of families and mutations

Family	Clinical syndrome	Neonatal Seizures		Mutation	Family previously reported (reference)
		Onset range (n)[a]	Latest offset		
1	BFNE	3-5d (3)	3m	*KCNQ2* c.1A>G (p.?)	18
2	BFNE	1-2d (2)	4m	*KCNQ2* c.2T>C (p.?)	18
3	BFNE	2-7d (6)	2w	*KCNQ2* c.63_66delGGTG (p.Val22Alafs*19)	15
4	BFNE	2-6d (2)	2w	*KCNQ2* c.204dupC (p.Lys69Glnfs*51)	18
5	BFNE	2-3d (3)	8m	*KCNQ2* c.340A>G (p.Thr114Ala)	
6	BFNE	3d, 4m (3)	5m	*KCNQ2* c.475G>A (p.Gly159Arg)	
7	BFNE	3-6d, 3m (5)	6m	*KCNQ2* c.610C>T (p.Gln204*)	
8	BFNE, Epileptic encephalopathy	2-4d (2)	2.5m	*KCNQ2* c.638G>A (p.Arg213Gln) Father 30% mosaic	17
9	BFNE	1-2d (3)	5m	*KCNQ2*.c.1054T>C (p.Ser352Pro)	
10	BFNE	1-5d (4)	3w	*KCNQ2* c.1057C>G (p.Arg353Gly)	18
11	BFNE	2-5d (4)	4m	*KCNQ2* c.1073C>T	

For Review Only

				(p.Ser358Phe)	
12	BFNE	1d (2)	?2m	*KCNQ2* c.1247+1G>A	
13	BFNE	1-5d (2)	6m	*KCNQ2* c.1342C>T (p.Arg448*)[b]	18
14	BFNE	2-3d (3)	4w	*KCNQ2* c.1418_19delTC (p.Leu473Argfs*47)	
15	BFNE	2-5d (7)	6m	*KCNQ2* c.1525+1G>A	18
16	BFNE	3-7d (6)	5m	*KCNQ2* c.1631+1G>A[c]	
17	BFNE	1-5d, 70d (12)	5m	*KCNQ2* c.1684_1685insGCCCT (p.Tyr562Cysfs*5)	13
18	BFNE	1-3d (3)	4m	*KCNQ2* c.1732A>G (p.Met578Val)	
19	BFNE	6d (1)	6d	*KCNQ2* c.1741C>T (p.Arg581*)[d]	
20	BFNE	1-4d (9)	4m	*KCNQ2* c.1764A>T (p.Arg588Ser)	18
21	BFNE	Neonatal (2)	?	*KCNQ2* c.1856_1886del31bp (p.Met619Argfs*13)	
22	BFNE	2-6d, 35d (4)	3m	*KCNQ2* c.1910T>G (p.Leu637Arg)	18
23	BFNE	5d, 4m (5)	4m	*KCNQ2* c.1-? c.993+?del	14
24	BFNE	2d (3)	15m	*KCNQ2* c.565-682_c.1295+?del	
25	BFNE	4-9d, <30d (6)	<1yr	*KCNQ2* c.474-940_c.1424+1582del	14

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26	BFNE	3-7d (3)	6m	*KCNQ2* c.474-940_c.1424+1582del	
27	BFNE	5-7d, 4m (3)	4m	*KCNQ2* c.565-?_c.1478+?(2)[e]	[14]
28	BFNE	1-2d (2)	9d	*KCNQ2* c.1479-768_c.1940+579del3018bp	[14]
29	BFNE	2-4d (4)	3m	*KCNQ3* c.1019G>T (p.Gly340Val)	
30	BFNE	3d, 3m (4)	6m	*SCN2A* c.3961G>A (p.Glu1321Lys)	
31	BFNE	2-3d (7)	3m	*SCN2A* c.4591C>A (p.Gln1531Lys)	
32	FNE + DD	2-18d (4)	19m	2q24.3 duplication	[16]
33	BFNE	2-7d, 62d (7)	3m	ND	
34	BFNE	1-5d (5)	6m	ND	
35	BFNE	1-3d (4)	4m	ND	
36	FNE + DD	3-10d (3)	4m	ND	

[a] n = number of family members with age of onset data available

[b] Mutation also reported in references [22; 38; 39]

[c] Mutation also reported in reference [40]

[d] Mutation also reported in reference [22]

[e] The insertion point of this duplication has not been experimentally determined, however it is predicted to be inserted within *KCNQ2* leading to a disruption of the gene.

Abbreviations: BFNE benign familial neonatal epilepsy; DD developmental delay; FNE familial neonatal epilepsy; d days; m months; w weeks; ND Not detected

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Figure titles and legends:

Figure 1 – Pedigrees of families with familial neonatal seizures.

A *KCNQ2* mutation positive families, **B** Families with mutations in other genes, **C** Unsolved families

Figure 2 – Recurrent patterns of seizures beyond neonatal and infantile period in *KCNQ2*-positive BFNE families.

Circles indicate single seizures; rectangles indicate multiple seizures in the time period. Length of line indicates age at last follow-up. Representation of seizure timing is approximate and generally based on historical recall.

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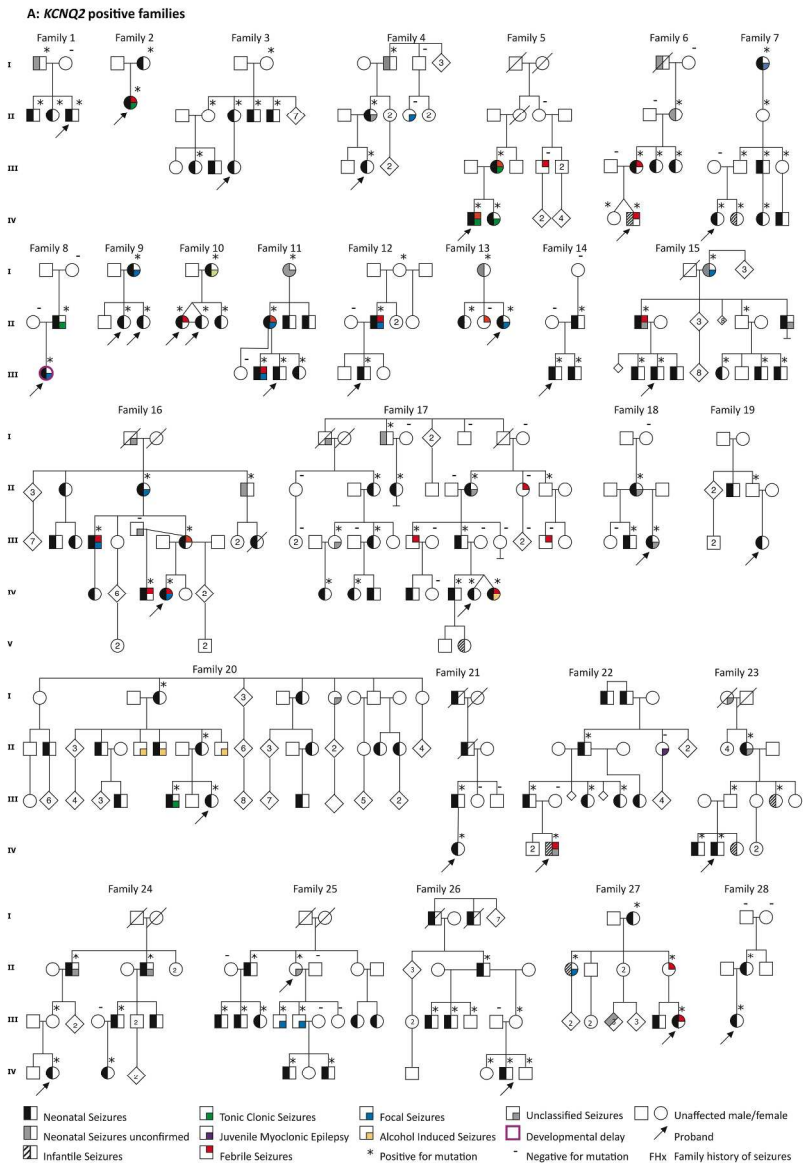
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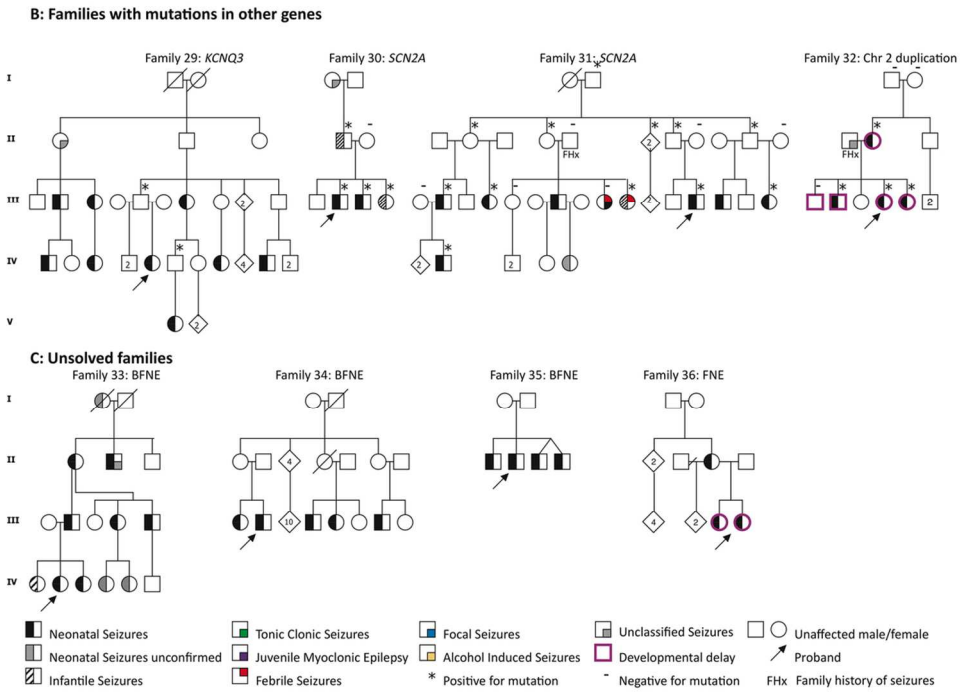
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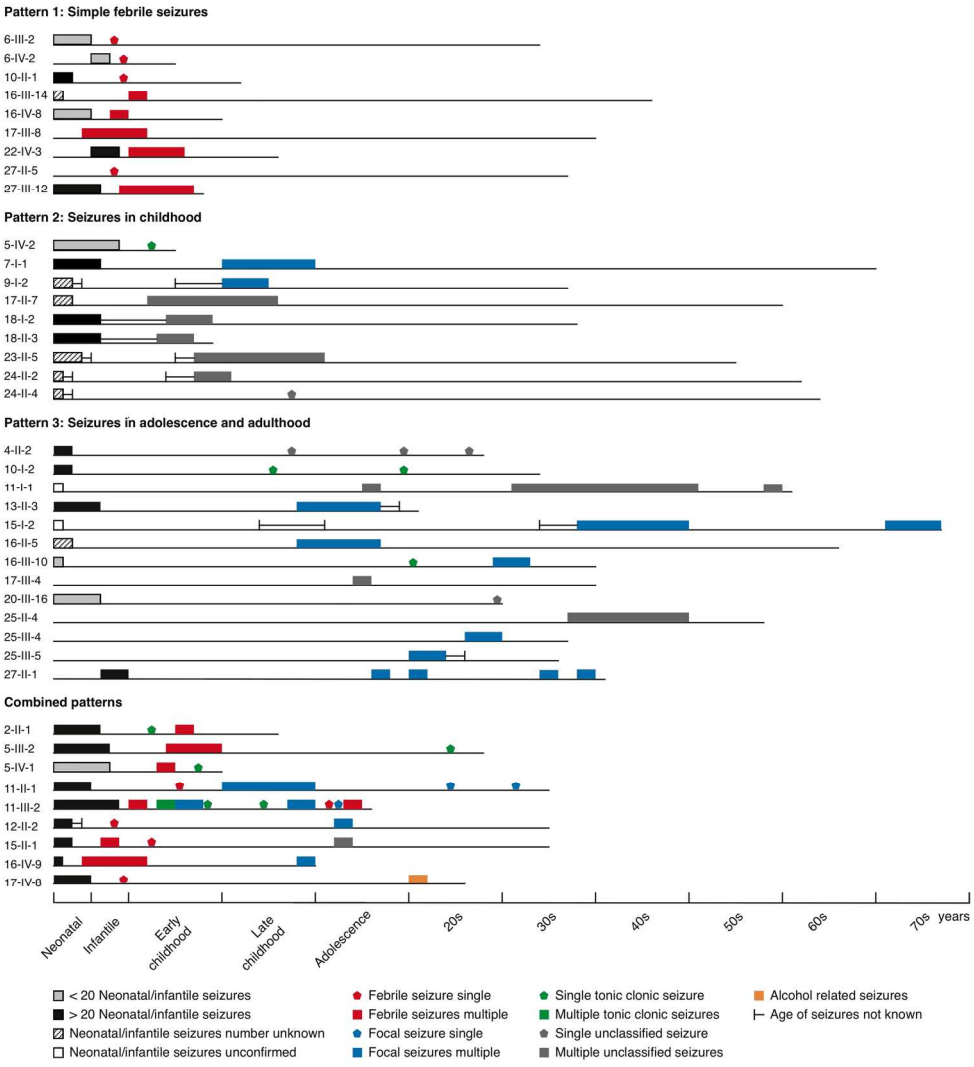
Pedigrees of families with familial neonatal seizures.
A) KCNQ2 mutation positive families
219x314mm (300 x 300 DPI)



Pedigrees of families with familial neonatal seizures.
B) Families with mutations in other genes, C) Unsolved families

111x80mm (300 x 300 DPI)

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Recurrent patterns of seizures beyond neonatal and infantile period in KCNQ2-positive BFNE families. Circles indicate single seizures; rectangles indicate multiple seizures in the time period. Length of line indicates age at last follow-up. Representation of seizure timing is approximate and generally based on historical recall.
184x199mm (300 x 300 DPI)