Proposal form for the evaluation of a genetic test for NHS Service Gene Dossier/Additional Provider

TEST – DISORDER/CONDITION – POPULATION TRIAD			
Submitting laboratory:	**London Institute of Neurology**	**Approved:**	**Sept 2013**

1. Disorder/condition – approved name and symbol as published on the OMIM database (alternative names will be listed on the UKGTN website)	Brain Channelopathy See Appendix 1
2. OMIM number for disorder/condition	See Appendix 1
3a. Disorder/condition – please provide, in laymen's terms, a brief (2-5 sentences) description of how the disorder(s) affect individuals and prognosis.	Pathogenic mutations in the genes on this panel have been associated with a group of overlapping group of episodic neurological disorders. This is a core clinical triad that make up this group and encompass episodic ataxia (EA), a neurologic condition characterized by spells of incoordination and imbalance, familial hemiplegic migraine (HM), which is characterized by an aura of hemiplegia that is always associated with at least one other aura symptom, hemisensory deficit, or aphasia (the disturbance in formulation and comprehension of language). The aura is followed by a moderate to severe headache. The third feature is kinesogenic dystonic which is posturing with exercise or sudden movements. Some of these genes are associated with epilepsy such as defects in PRRT2 or CACNB4, but this is unusual.
3b Disorder/condition – if required please expand on the description of the disorder provided in answer to Q3a.	Given in 3a above
4. Disorder/condition – mode of inheritance	Autosomal Dominant
5. Gene – approved name(s) and symbol as published on HGNC database (alternative names will be listed on the UKGTN website)	See Appendix 1
6a. OMIM number for gene(s)	See Appendix 1
6b HGNC number for gene(s)	See Appendix 1
7a. Gene – description(s)	**ATP1A2** encodes the alpha-2 catalytic subunit isoform of the Na(+),K(+)-ATPase of an integral membrane protein responsible for establishing and maintaining the electrochemical gradients of Na and K ions across the plasma membrane. Mutations in this gene have been found to be associated with familial basilar or hemiplegic migraines and a rare syndrome known as alternating hemiplegia of childhood. **ATP1A3** encodes the alpha-3 catalytic subunit isoform of the Na(+),K(+)-ATPase of an integral membrane protein responsible for establishing and maintaining the electrochemical gradients of Na and K ions across the plasma membrane. Mutations in this gene have been found to be associated with alternating hemiplegia of childhood-2 (AHC2).

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	CACNA1A encodes the transmembrane pore-forming subunit of the P/Q-type or CaV2.1 voltage-gated calcium channel. Mutations in this gene are associated with familial hemiplegic migraine and episodic ataxia type 2 (EA2). **CACNB4** encodes the beta-4 isoform of the regulatory beta subunit of voltage-activated Ca(2+) channels. Mutations in this gene have been associated with idiopathic generalized epilepsy (IGE) and juvenile myoclonic epilepsy (JME). **KCNA1** encodes subunit 1 of voltage-dependent K+ channels. Mutations in this gene have been associated with myokymia with periodic ataxia (EA1). **KCNK18** encodes a two-pore domain (K2P) potassium channel, which gives rise to background, or leak, potassium conductance and it regulates diverse cellular functions by adjusting both the resting membrane potential and excitability, its activity is regulated by intracellular calcium. Mutations in this gene have been found to be associated with migraine with aura. **PNKD** encodes a protein which functions in a pathway to detoxify methylglyoxal, a compound present in coffee and alcoholic beverages and produced as a by product of oxidative stress. Mutations in this gene have been associated with the movement disorder paroxysmal non-kinesigenic dyskinesia. **PRRT2** encodes a protein which interacts with SNAP25, a synaptosomal membrane protein. Mutations in this gene are associated with episodic kinesigenic dyskinesia or dystonia and occasionally hemiplegic migraine and epilepsy. **SCN1A** encodes the large central pore-forming glycosylated alpha subunit of the voltage-gated sodium ion channel essential for the generation and propagation of action potentials, chiefly in nerve and muscle. Mutations in this gene have been associated with several epilepsy, convulsion and migraine disorders. **SLC1A3** encodes a protein that is a high-affinity sodium-dependent transporter molecule that regulates neurotransmitter concentrations at the excitatory glutamatergic synapses of the mammalian central nervous system. Mutations in this gene are associated with episodic ataxia type 6 (EA6). **SLC2A1** encodes the major glucose transporter in brain, placenta, and erythrocytes. Mutations in this gene have been found to be associated with paroxysmal exertion-induced dyskinesia.
7b. Number of amplicons to provide this test (molecular) or type of test (cytogenetic)	Overall target size 32.751kbp

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7c. GenU band that this test is assigned to for index case testing	H; 40
8. Mutational spectrum for which you test including details of known common mutations	Single nucleotide variants: Missense, nonsense, silent, splice-site, intronic variants flanking exons. Small insertions/deletions.
9a. Technical method(s)	Mutation screening of the coding regions and intron-exon boundaries of the genes listed using next generation sequencing by synthesis approach: Targeted enrichment of the 11 genes by the Illumina TruSeq Custom Amplicon (TSCA) method followed by analysis on an Illumina MiSeq. Demultiplexed fastQ files are generated using MiSeq Reporter software v2.0. Paired-end reads of each sample are aligned to the human genome, hg19, in NOVOALOGIN software. Read pileup and variant detection is performed in SAMTOOLS. Identified variants are annotated in ANNOVAR to generate a mutation report. Coverage of the targeted regions on a per sample basis is generated using in-house developed software called CovCheck and data is also analysed using NextGENe software and GenomeBrowse1.1.1. All bases analysed are covered by a minimum of 100 reads with an average of 500. Sanger sequencing is used to confirm any pathogenic mutations detected and to fill in any gaps as necessary.
9b If a panel test using NGS please state if it is a conventional panel or a targeted exome test.	Conventional Custom Amplicon Panel (Illumina TSCA) Targeted gene panel test
9c. Panel/targeted exome Tests **i) Do the genes have 100% coverage? If not what is the strategy for dealing with the gaps in coverage?**	All coding exons of the genes in the panel are covered except for the following: ATP1A3 exons 15,16,17 and 18; CACNA1A exons 37 and 36; CACNB4 exon 3 and SCN1A exons 2 and 15. Following each run, coverage for each exon is assessed using the NextGENe software package which identifies exons that have reduced or absent coverage. Untargeted exons, failed exons or those with inadequate coverage are repeated using Sanger sequencing. This may not be performed for all gaps if a genetic diagnosis has been reached and will be decided on a case-by-case basis.
ii) Does the test include MLPA?	Yes an additional MLPA test is run simultaneously at present for all the coding exons of CACNA1A, ATP1A2, KCNA1 and SCN1A. An analysis pipeline is being developed that will enable whole exon deletions and duplications to be detected.
iii) Does this use sanger sequencing or Next Generation Sequencing (NGS)?	NGS Primarily NGS, then Sanger sequencing to confirm variants and fill in gaps.
iv) If NGS is used, does the lab adhere to the Practice Guidelines for NGS?	Yes
10 Is the assay to be provided by the lab or is it to be outsourced to another provider?	To be provided by our lab

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If to be outsourced, please provide the name of the laboratory.	
11. Validation process Please explain how this test has been validated for use in your laboratory or submit your internal validation documentation	Two 96 illumina custom true seq amplicon panels containing these genes have been run in this laboratory on a research basis. In each panel we included 24 blinded samples containing between them 288 known variants detected by Sanger sequencing, the other samples were research samples for testing. 15 pathogenic mutations detected in samples on the panel that had not previously been analysed were all subsequently confirmed to be true using Sanger sequencing. The mutations detected included missense, silent, nonsense, splice site, a 2bp deletion and a 1bp and 2 bp insertion. A third panel containing these genes has been run as a diagnostic service and final analysis is in process. In our laboratory to date 6 different Illumina TSCA panels (a total of over 1000 different amplicons) have been run and analysed on a research basis for 95 samples each. Over 300 blinded samples with 629 known variants detected by Sanger sequencing were analysed on these panels and all variants were detected. These included missense, nonsense, silent, splice mutations, flanking intronic variants and small indels up to 20bp in length. Also 33 pathogenic mutations detected in samples on the panels not previously analysed were all subsequently confirmed to be true using Sanger sequencing. The data from these 6 panels demonstrate that all previously known pathogenic mutations and polymorphisms can be detected using custom amplicon next generation sequencing panels.
12a. Are you providing this test already?	☒ **No** ☐ **Yes** Not all of these genes are offered on a diagnostic basis but we currently offer diagnostic testing for mutations in CACNA1A, KCNA1 and SCN1A using Sanger sequencing which are listed on UKGTN. No reports using NGS technology have been issued to date for these genes.
12b. If yes, how many reports have you produced? **Please provide the time period in which these reports have been produced and whether in a research or a full clinical diagnostic setting.**	CACNA1A: 104 from May 2011 to December 2012 KCNA1: 210 from May 2007 to December 2012 SCN1A: 112 from January 2010 to December 2012 No reports using NGS technology have been issued to date for these genes.
12c. Number of reports mutation positive	CACNA1A: 29 positive reports KCNA1: 20 positive reports SCN1A: 30 positive reports
12d. Number of reports mutation negative	CACNA1A: 75 negative reports KCNA1: 190 negative reports SCN1A: 82 negative reports
13. For how long have you been providing this service?	CACNA1A: sequencing of the entire coding region and dosage since May 2011

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	KCNA1: May 2007 SCN1A: January 2010 No reports using NGS technology have been issued to date for these genes.
14a. Is there specialised local clinical/research expertise for this disorder?	☐ **No** ☒ **Yes**
14b. If yes, please provide details	Professor Henry Houlden and Professor Michael Hanna have research groups investigating mutations in brain channels both genetically and functionally. Professor Henry Houlden runs a Neurogenetics clinic at The National Hospital for Neurology along with Professor Nicholas Wood and sees many of these patients and families as does Professor Michael Hanna in his Channel Clinic; Dr Paola Giunti in the Ataxia Clinic and there is a busy headache clinic and epilepsy service. Professor Nicholas Wood also runs a joint paediatric Ataxia clinic in Great Ormond Street with Dr Lucinda Carr.
15. Are you testing for other genes/disorders/conditions closely allied to this one? Please give details	Spinocerebellar ataxia: SCA1,2,3,6,7,12,17 are currently offered by this laboratory Inherited epilepsy: SCN1A sequencing and MLPA are currently offered by this laboratory.
16. Based on experience what will be the national (UK wide) activity, per annum, for:	
16a. Index cases	155 index cases were referred to this laboratory in 2012, but we would expect this to increase with the increased number of genes available
16b. Family members where mutation is known	38 family members of index cases were referred to this laboratory in 2012, again with comprehensive testing we expect this to increase
17a. Does the laboratory have capacity to provide the expected national activity?	Yes
17b. If your laboratory does not have capacity to provide the full national need please could you provide information on how the national requirement may be met. For example, are you aware of any other labs (UKGTN members or otherwise) offering this test to NHS patients on a local area basis only? This question has been included in order to gauge if there could be any issues in equity of access for NHS patients. It is appreciated that some laboratories may not be able to answer this question. If this is the case please write "unknown".	
18. Please justify the requirement for another laboratory to provide this test e.g. insufficient national capacity.	There is a very limited national capacity to do any of these tests, as far as we know we will be the only laboratory to offer ATP1A2, ATP1A3, PRRT2, CACNB4 and KCNK18 in the UK.

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EPIDEMIOLOGY	
19a. Estimated prevalence of condition in the general UK population	9-10/100,000
19b. Estimated incidence of condition in the general UK population Please identify the information on which this is based	**2/100,000** Jen et al (2007) *Brain*. **130**(Pt 10):2484-93. And from data collected from our clinics over 10 years.
20. Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	2/100,000 Jen et al (2007) *Brain*. **130**(Pt 10):2484-93. And from data collected from our clinics over 10 years.
21. Estimated penetrance Please identify the information on which this is based	90% penetrance but there is reduced clinical expression in 10% of cases. This is based on the unpublished NHNN research series. See also for PRRT2: Gardiner et al (2012) *Neurology*. **79**:2115-21
22. Estimated prevalence of condition in the population of people that meet the Testing Criteria.	Unknown

INTENDED USE

23. Please tick either yes or no for each clinical purpose listed.

Panel Tests: a panel test would not be used for pre symptomatic testing, carrier testing and pre natal testing as the familial mutation would already be known in this case and the full panel would not be required.

Diagnosis	☒ **Yes**	☐ **No**
Treatment	☒ **Yes**	☐ **No**
Prognosis & management	☒ **Yes**	☐ **No**
Presymptomatic testing (n/a for panel tests)	☐ **Yes**	☐ **No**
Carrier testing for family members (n/a for panel tests)	☐ **Yes**	☐ **No**
Prenatal testing (n/a for panel tests)	☐ **Yes**	☐ **No**

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TEST CHARACTERISTICS

24. Analytical sensitivity and specificity This should be based on your own laboratory data for the specific test being applied for or the analytical sensitivity and specificity of the method/technique to be used in the case of a test yet to be set up.

Analytical sensitivity:
288/288 SNPS (including missense, silent, nonsense, intronic variants and small indels up to 2bp) previously identified with Sanger sequencing were all correctly detected on custom amplicon panels of these genes, suggesting a sensitivity of 100%. Also 15/15 pathogenic mutations detected in samples not previously analysed by Sanger sequencing were detected and subsequently confirmed by Sanger sequencing again suggesting a sensitivity of 100%.

Analytical specificity:

Close to 100%

25. Clinical sensitivity and specificity of test in target population The *clinical sensitivity* of a test is the probability of a positive test result when condition is known to be present; the *clinical specificity* is the probability of a negative test result when disorder is known to be absent. The denominator in this case is the number with the disorder (for sensitivity) or the number without condition (for specificity).

Clinical Sensitivity: 30% (Many genes remain unknown)

Clinical Specificity: Close to 100%

26. Clinical validity (positive and negative predictive value in the target population) The *clinical validity* of a genetic test is a measure of how well the test predicts the presence or absence of the phenotype, clinical condition or predisposition. It is measured by its *positive predictive value* (the probability of getting the condition given a positive test) and *negative predictive value* (the probability of not getting the condition given a negative test).

Positive Predictive Value: 99%

Negative Predictive Value: 70%

27. Testing pathway for tests where more than one gene is to be tested Please include your testing strategy if more than one gene will be tested and data on the expected proportions of positive results for each part of the process. Please illustrate this with a flow diagram. This will be added to the published Testing Criteria.

This will be the first-line test for these referrals.

CLINICAL UTILITY

28. How will the test change the management of the patient and/or alter clinical outcome?

The test will be performed to achieve a confirmed diagnosis and to aid in making informed treatment decisions and to improve long term management. An example of this is patients in the early stages of disease in their late teens and 20s often require higher doses of drugs such as Diamox and patients find ways and diets to reduce attacks, whereas later on the disease tends to burn out and require less if any treatment and they can often manage more effectively. Currently only 3 of the genes on this panel are analysed sequentially in this laboratory which is laborious, expensive and time consuming. With this NGS panel test, the genes are analysed simultaneously. As a significant proportion of patients have an overlapping clinical phenotype, this will allow for a more rapid genetic confirmation of diagnosis at a fraction of the present cost.

29. Benefits of the test for the patient & other family members Please provide a summary of the overall benefits of this test.

The test will greatly improve the speed and accuracy of diagnosis. It will reduce the number of repeat genetic tests that are required. An early confirmed diagnosis will allow initiation of treatment early in the disease course which will allow better management of symptoms. A positive test will allow earlier treatment of appropriate drugs as patients are often given ineffective medications.

30. What will be the consequences for patients and family members if this test is not approved?

If this test is not approved, it would take longer for a confirmed diagnosis to be obtained. This would expose patients and family members to continued uncertainty and would delay treatment.

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31. Is there an alternative means of diagnosis or prediction that does not involve molecular diagnosis? If so (and in particular if there is a biochemical test), please state the added advantage of the molecular test.

There is no alternative means of accurate diagnosis.

32. Please describe any specific ethical, legal or social issues with this particular test.

Testing should only be performed when the patient (or their legal guardian) have understood and consented to the test. Results to date suggest that variants of uncertain significance will be identified in less than 10% of cases which will be discussed and explained within the Neurogenetics Clinic.

33. Only complete this question if there is previously approved Testing Criteria and you do not agree with it.

Please provide revised Testing Criteria on the Testing Criteria form and explain here the changes and the reasons for the changes.

34. List the diagnostic tests/procedures that an index case no longer needs if this genetic test is available.

	Type of test	Cost (£)
Costs and type of imaging procedures	MRI	£750
Costs and types of laboratory pathology tests (other than molecular/cyto genetic test proposed in this gene dossier)	Blood, antibodies	£500
Costs and types of physiological tests (e.g. ECG)	EEG, special NCS	£250 + £250
Cost and types of other investigations/procedures (e.g. biopsy)	Muscle biopsy	£900
Total cost tests/procedures no longer required		**£2650**

35. Based on the expected annual activity of index cases (Q15a), please calculate the estimated annual savings/investments based on information provided in Q33.

Number of index cases expected annually	(a) 155
Cost to provide tests for index cases if the genetic test in this gene dossier was not available (see Q34)	(b) £2650
Total annual costs pre genetic test	(a) x (b) = (c) = £410,750
Total annual costs to provide genetic test	(a) x cost of genetic testing for index case = (d) = 155 x £600=£93,000
Total savings	(c) – (d)= 410,750-93,000=£317,750

36. REAL LIFE CASE STUDY

In collaboration with the clinical lead, describe TWO real case examples:

1. **prior to availability of genetic test**
2. **post availability of genetic test**

to illustrate how the test improves patient experience and the costs involved.

Case example one – pre genetic test

1. A case with a good history for an episodic neurological disorder with ataxia and hemiplegic migraine. Both conditions were hard to manage and required in depth investigation and treatment trials. The genetic testing of CACNA1A confirmed a heterozygous defect which was likely from the father who was dead but had atypical migraine headaches.
   The result was important for many reasons and had an impact on treatment as he responded to acetazolamide, a drug that is often low on the treatment list.
2. This patient had a history of exercise induced movement disorder and epilepsy as a child. He was investigated in depth with no cause identified. He responded well to treatment with carbamazepine. The genetic test confirmed a PRRT2 insertion in him and his mother. Again the result was important for many reasons but the exact diagnosis gave an important reason to continue this treatment.

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Carbamazepine is effective in PRRT2 associated paroxysmal dyskinesia but the diagnosis gave reassurance this was the correct management as this drug will be needed for many years for this condition.

PRE GENETIC TEST COSTS

	Type of test	Cost
Costs and type of imaging procedures	MRI	£750
Costs and type of laboratory pathology tests	Blood, antibodies	£500
Costs and type of physiological tests (e.g. ECG)	EEG, special NCS	£250 + £250
Cost and type of other investigations/procedures (e.g. biopsy)	Muscle biopsy	£900
Cost outpatient consultations (genetics and non genetics)	Neurology and genetics	2 x £550
Total cost pre genetic test		**£ 3750**

Case example two – post genetic test

This would be the same as above but the number of investigations would be reduced and the time taken to diagnosis would be much faster. The treatment of these problems is often different and a genetic diagnosis would allow much faster treatment.

POST GENETIC TEST COSTS

	Type of test	Cost
Costs and type of imaging procedures		
Costs and types laboratory pathology tests (other than molecular/cyto genetic proposed in this gene dossier)	Monitor treatment such as renal function	£50/year
Cost of genetic test proposing in this gene dossier	Episodic panel	£530
Costs and type of physiological tests (e.g. ECG)		
Cost and type of other investigations/procedures (e.g. biopsy)		
Cost outpatient consultations (genetics and non genetics)	Neurogenetics clinic	£550/year
Total cost post genetic test		**£ 1130**

37. Estimated savings between two case examples described £ 2620

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UKGTN Testing Criteria

Test name: **Brain Channelopathy Panel 11 Gene Panel**	
Approved name and symbol of disorder/condition(s): Brain Channelopathy See Appendix 1 **Approved name and symbol of gene(s):** See Appendix 1	**OMIM number(s):** See Appendix 1 **OMIM number(s):** See Appendix 1

Patient name:	**Date of birth:**
Patient postcode:	**NHS number:**
Name of referrer:	
Title/Position:	**Lab ID:**

Referrals will only be accepted from one of the following:	
Referrer	**Tick if this refers to you.**
Consultant Neurologist	
Consultant Paediatric Neurologist	
Consultant Clinical Geneticist	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:	
Criteria	**Tick if this patient meets criteria**
A clear clinical history of an episodic ataxia **OR**	
Hemiplegic migraine with the following features: • Fulfils criteria for Migraine with Aura (MA) • Aura including some degree of hemiparesis and may be prolonged • At least one first-degree relative with identical attacks **OR**	
Paroxysmal dyskinesia	

Additional Information:
For panel tests: At risk family members where familial mutation is known do not require a full panel test but should be offered analysis of the known mutation

If the sample does not fulfil the clinical criteria or you are not one of the specified types of referrer and you still feel that testing should be performed please contact the laboratory to discuss testing of the sample.

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Testing Criteria Appendix 1
Conditions in panel test

OMIM standard name of condition and symbol	OMIM number	HGNC standard name and symbol of the gene	HGNC number	OMIM number	References or locus specific database links
MIGRAINE, FAMILIAL HEMIPLEGIC, 2; FHM2	602481	ATPase, Na+/K+ TRANSPORTING, ALPHA-2 POLYPEPTIDE; ATP1A2	**800**	182340	http://www.LOVD.nl/ATP1A2
ALTERNATING HEMIPLEGIA OF CHILDHOOD 1; AHC1	104290	ATPase, Na+/K+ TRANSPORTING, ALPHA-2 POLYPEPTIDE; ATP1A2	**800**	182340	http://www.LOVD.nl/ATP1A2
DYSTONIA 12; DYT12	128235	ATPase, Na+/K+ TRANSPORTING, ALPHA-3 POLYPEPTIDE; ATP1A3	**801**	182350	11 families with mutations in this gene have been described on OMIM (de Carvalho Aguiar et al 2004; Brashear et al 2007 and Blanco-Arias et al 2009).
ALTERNATING HEMIPLEGIA OF CHILDHOOD 2; AHC2	614820	ATPase, Na+/K+ TRANSPORTING, ALPHA-3 POLYPEPTIDE; ATP1A3	**801**	182350	Heinzen et al. (2012) Nature Genet. 44: 1030-1034 estimate that pathogenic mutations in this gene may account for up to 74% of patients with sporadic, typical AHC
EPISODIC ATAXIA, TYPE 2; EA2	108500	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, P/Q TYPE, ALPHA-1A SUBUNIT; CACNA1A	**1388**	601011	http://www.LOVD.nl/CACNA1A
MIGRAINE, FAMILIAL HEMIPLEGIC, 1; FHM1	141500	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, P/Q TYPE, ALPHA-1A SUBUNIT; CACNA1A	**1388**	601011	http://grenada.lumc.nl/LOVD2/FHM/home.php?select_db=CACNA1A
EPISODIC ATAXIA, TYPE 5; EA5	613855	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, BETA-4 SUBUNIT; CACNB4	**1404**	601949	1 family described on OMIM Escayg et al. 2000; 1 index case identified in house
EPILEPSY, IDIOPATHIC GENERALIZED, SUSCEPTIBILITY TO, 9; EIG9	607682	CALCIUM CHANNEL, VOLTAGE-DEPENDENT, BETA-4 SUBUNIT; CACNB4	**1404**	601949	2 families described on OMIM Escayg et al. 2000
EPISODIC ATAXIA, TYPE 1; EA1	160120	POTASSIUM CHANNEL, VOLTAGE-GATED, SHAKER-RELATED SUBFAMILY, MEMBER 1 (EPISODIC ATAXIA WITH MYOKYMIA); KCNA1	**6218**	176260	15 index cases with different pathogenic mutations are described on OMIM
MIGRAINE, WITH OR WITHOUT AURA, SUSCEPTIBILITY TO,	613656	POTASSIUM CHANNEL, SUBFAMILY K,	**19439**	613655	1 family reported on OMIM Lafreniere et al 2010; 2 index cases identified in house

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OMIM standard name of condition and symbol	OMIM number	HGNC standard name and symbol of the gene	HGNC number	OMIM number	References or locus specific database links
13; MGR13		MEMBER 18; KCNK18			
PAROXYSMAL NONKINESIGENIC DYSKINESIA 1; PNKD1	118800	PAROXYSMAL NONKINESIGENIC DYSKINESIA; PNKD	**9153**	609023	14 families with pathogenic mutations reported on OMIM
CONVULSIONS, FAMILIAL INFANTILE, WITH PAROXYSMAL CHOREOATHETOSIS; ICCA	602066	PROLINE-RICH TRANSMEMBRANE PROTEIN 2; PRRT2	**30500**	614386	>63 families described on OMIM
EPISODIC KINESIGENIC DYSKINESIA 1; EKD1	128200	PROLINE-RICH TRANSMEMBRANE PROTEIN 2; PRRT2	**30500**	614386	>47 families described on OMIM
SEIZURES, BENIGN FAMILIAL INFANTILE, 2; BFIS2	605751	PROLINE-RICH TRANSMEMBRANE PROTEIN 2; PRRT2	**30500**	614386	>57 families described on OMIM
DRAVET SYNDROME	607208	SODIUM CHANNEL, NEURONAL TYPE I, ALPHA SUBUNIT; SCN1A	**10585**	182389	http://www.molgen.ua.ac.be/SCN1AMutations/Home/Default.cfm
GENERALIZED EPILEPSY WITH FEBRILE SEIZURES PLUS, TYPE 2; GEFSP2	604403	SODIUM CHANNEL, NEURONAL TYPE I, ALPHA SUBUNIT; SCN1A	**10585**	182389	http://www.molgen.ua.ac.be/SCN1AMutations/Home/Default.cfm
MIGRAINE, FAMILIAL HEMIPLEGIC, 3; FHM3	609634	SODIUM CHANNEL, NEURONAL TYPE I, ALPHA SUBUNIT; SCN1A	**10585**	182389	http://www.molgen.ua.ac.be/SCN1AMutations/Home/Default.cfm 5 families described on OMIM
EPISODIC ATAXIA, TYPE 6; EA6	612656	SOLUTE CARRIER FAMILY 1 (GLIAL HIGH AFFINITY GLUTAMATE TRANSPORTER), MEMBER 3; SLC1A3	**10941**	600111	2 families reported on OMIM Jen et al 2005; de Vries et al 2009
GLUT1 DEFICIENCY SYNDROME 2; GLUT1DS2	612126	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 1; SLC2A1	**11005**	138140	6 families described on OMIM Weber et al 2008; Suls et al 2008; Schneider et al 2010 6 index cases identified in house
EPILEPSY, IDIOPATHIC GENERALIZED, SUSCEPTIBILITY TO, 12; EIG12	614847	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 1; SLC2A1	**11005**	138140	2 families reported on OMIM Suls et al 2008; Striano et al 2012 1 index case identified in house
GLUT1 DEFICIENCY SYNDROME 1; GLUT1DS1	606777	SOLUTE CARRIER FAMILY 2 (FACILITATED GLUCOSE TRANSPORTER), MEMBER 1; SLC2A1	**11005**	138140	6 families described on OMIM Seidner et al 1998; Wang et al 2000; Klepper et al 2001; Brockmann et al 2001 3 index cases identified in house

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