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

Test – Disease – Population Triad

Disease – name and description (please provide any alternative names you wish listed) (A)-Testing Criteria	Episodic Ataxia type 1 (EA1) Episodic Ataxia with myokymia (EAM) KCNA1 related episodic ataxia Ataxia, episodic with myokymia (AEM/AEMK) Paroxymal Ataxia with Neuromyotonia, Hereditary Myokymia with Periodic Ataxia Myokymia EA with partial epilepsy EA without myokymia Isolated severe neuromyotonia Isaacs-Mertens syndrome Type 1 episodic ataxia (EA1) is characterized by brief (generally less than 15 minutes) attacks of ataxia and dysarthria induced by emotion, illness, stress or kinesigenic stimulation, with myokymia both during and between attacks. Myokymia affects the arms, face hands and legs and can be so mild as to be subclinical. Additional features can include nausea, dysarthria, epilepsy and visual blurring with onset commonly within the 1st decade. Attacks may be helped by the use of acetazolamide (a carbonic anhydrase inhibitor) or carbamazepine (an anti epilepsy drug) although response to different medications may be mutation specific.
OMIM number for disease	160120 (EA1)
Gene – name and description (please provide any alternative names you wish listed)	The *KCNA1* (Kv1.1) gene codes for a voltage gated potassium channel. It has only a single coding exon which is ~1.5kb in size. The gene is located at 12p13.
OMIM number for Gene	176260
Mutational spectrum for which you test	Analysis covers the whole coding region of exon 1 performed in 4 overlapping amplicons. This analysis will detect all point mutations (missense, nonsense, frameshift, splice site [at intron/exon boundaries], and small insertions and deletions) and will detect 100% of published mutations.
Technical Method (s)	Bidirectional fluorescent genomic DNA sequencing.
Validation Process Note please explain how this test has been validated for use in your laboratory	DNA sequencing has been extensively validated within the laboratory against scanning techniques (SSCP, CSGE) and is the main route for mutation detection within the lab. We participate in EQA (UKNEQAS and EMQN, including the sequencing scheme).
Are you providing this test already? If yes, how many reports have you produced? Please give the number of mutation positive/negative samples you have reported	No

For how long have you been providing this service?	
Is there specialised local clinical/research expertise for this disease?	**Yes √** | **No** | **Please provide details** The ataxia clinic at the Department of Neurology, Royal Hallamshire Hospital (Sheffield, UK) was established 12 years ago and has recently been accredited by Ataxia UK as one of three UK centres of excellence (the other 2 being in Northern Ireland and London). Dr Marios Hadjivassiliou, who runs the ataxia clinic, looks after over 500 patients with progressive ataxia, the majority of whom are under regular follow-up. He is also involved in a number of research projects in ataxia.
Are you testing for other genes/diseases closely allied to this one? Please give details	We currently run a service for another of the episodic ataxias; EA2. EA2 and EA1 are both associated with paroxysmal attacks of ataxia; however, whereas the attacks seen in EA1 are generally short (seconds or minutes), those seen in EA2 usually last for hours or days. In addition to ataxia, EA1 is also associated with myokymia both during and between attacks. Myokymia is not seen in EA2 but nystagmus, which does not occur in EA1, can be misinterpreted as myokymia and as such there is a degree of clinical overlap. In addition, we also provide a diagnostic service for the following diseases involved in hereditary ataxia: SCA 1, 2, 3, 6, 7, 17, Friedreich ataxia and Dentatorubral-Pallidoluysian Atrophy (DRPLA).
Your Activity How many tests do you (intend to) provide annually in your laboratory?	Our service for EA2 has been operating for almost 12 months and so far around 80 referrals have been received. Based on the presumption that some clinicians will request EA1 testing if no EA2 associated mutations are identified and that patients are likely to be referred solely for EA1 the annual referral rate is likely to be around 50.
Based on experience how many tests will be required nationally (UK)? Please identify the information on which this is based	Although impossible to determine how many tests will be required nationally (also see above), since sequence analysis of *KCNA1* is also reportedly available at the Institute of Neurology, Queen Square, London, we would expect to be referred half of the tests required nationally.

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	The minimum estimated prevalence of progressive ataxias in the UK is 10 per 100,000 (Muzaimi *et al*., 2004 *J Neurol Neurosurg Psychiatry* **75**: 1129-34). The estimated prevalence of autosomal dominant ataxias is 1 in 12,500 (Craig *et al*., 2004 *Ann Neurol* **55**: 752-5). Out of 500 patients with progressive ataxia assessed by Dr Hadjivassiliou over the last 12 years, there are 10 patients with a history suggestive of episodic ataxia. Of these 5 have genetically confirmed EA2. The remaining may have EA1 which suggests a maximum prevalence amongst ataxias of less than 1%.
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	The prevalence of EA1 can only be estimated roughly. Only approximately 20 families have been described in the literature. Two different studies describing two mutations in the state of Oregon (approximately 2.5 million inhabitants) and three different mutations in the Netherlands (approximately 16 million inhabitants) suggests a prevalence of 1 in 500,000. However the actual prevalence may well be considerably higher as the disorder may remain unrecognised in many families (Handbook of Ataxia Disorders, 2000; Thomas Klockgether). Based on a prevalence of 1 in 500,000 the estimated allele frequency is 1 in 1,000,000.
Estimated penetrance Please identify the information on which this is based	The penetrance of *KCNA1* mutations is not currently known however based on functional studies of mutations seen to date (Maylie *et al;* 2002; *J. Neuroscience*; **22**:4786-4793) it is likely to be high.
Target Population The essential clinical or family history features defining the target population must be described. (C)-Testing Criteria	Type 1 episodic ataxia (EA1) is characterized by brief (generally less than 15 minutes) attacks of ataxia and dysarthria induced by emotion, illness, stress or kinesigenic stimulation, with myokymia both during and between attacks. Myokymia affects the arms, face hands and legs and can be so mild as to be subclinical. Additional features can include nausea, dysarthria, epilepsy and visual blurring with onset commonly within the 1st decade. Attacks may be helped by the use of acetazolamide (a carbonic anhydrase inhibitor) or carbamazepine (an anti epilepsy drug) although response to different medications may be mutation specific (Zuberi et al; Brain 1999 122:817-825.). It is inherited as an autosomal dominant disease and therefore there is often a family history of similar symptoms, compatible with an autosomal dominant mode of inheritance. Electromyographic studies will detect the presence of myokymia in the majority of affected individuals and can be useful to differentiate between EA1 and EA2, although not all individuals with EA1 have myokymia. Clinically the episodic ataxias are well characterised and differ from other genetic ataxias because of their episodic nature. Thus the testing criteria will be based purely on the clinical history which is distinct. The presence of family history may also increase the probability of EA. The target population will, however, be limited to patients with manifest disease and family members where appropriate. Gene mutations have been detected in individuals from different ethnic backgrounds and the testing will therefore not be limited to a particular ethnic group.

Estimated prevalence of disease in the target population	Please see above "Estimated prevalence of disease in the general UK population".

Intended Use (Please use the questions in Annex A to inform your answers)

Please tick the relevant clinical purpose of testing	**YES**	**NO**
Diagnosis	√	
Treatment	√	
Prognosis & Management	√	
Presymptomatic testing	√	
Risk Assessment - but not prenatal	√	

Test Characteristics

Analytical sensitivity and specificity	Sensitivity of DNA sequencing is over 95%. Since all mutations are checked in two separate amplicons, specificity is 100% where the mutation or type of mutation has been previously reported. Where the change is novel, it may be necessary to carry out family / RNA / population studies and it still may not be possible to reach a conclusion.
Clinical sensitivity and specificity of test in target population The *clinical sensitivity* of a test is the probability of a positive test result when disease is known to be present; the *clinical specificity* is the probability of a negative test result when disease is known to be absent. The denominator in this case is the number with the disease (for sensitivity) or the number without disease (for specificity)	DNA sequencing has a high clinical specificity. The *KCNA1* gene does have a number of known variants in the coding sequence, some of which are known to be associated with an EA1 phenotype. All common SNPs will be analysed by looking at allele frequency and, if necessary, in-house unclassified variant forms will be completed to distinguish between polymorphisms and mutations.
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 disease or predisposition. It is measured by its *positive predictive value* (the probability of getting the disease given a positive test) and *negative predictive value* (the probability of not getting the disease given a negative test). The denominator in this case is the number of people with a positive or a negative test respectively - not the number with or without the disease. The clinical validity may be calculated knowing the sensitivity and the specificity and the prevalence of the disease in the population being studied. Positive and negative predictive values depend critically on the prevalence of the disease in the test population	The penetrance of *KCNA1* mutations is not known and therefore the positive predictive value can not be calculated. In families with a known *KCNA1* mutation, the negative predictive value when testing asymptomatic family members is expected to be close to 100%

Clinical utility of test in target population (Please refer to Appendix A)	
Please provide a full description of the clinical care pathway for those individuals undergoing testing. This should include details of which medical specialties will be able to refer for testing.	In the Trent region, patients suspected of having EA1 will be referred to the ataxia clinic (Neurology Department, Royal Hallamshire Hospital, Sheffield, UK). Requests from other UK regions are likely to be initiated by consultant neurologists or by consultant clinical geneticists. Our understanding is that there is only one other laboratory in the UK offering this service, and there is very limited availability world-wide.
(B)-Testing Criteria	Initiation of testing for EA1 will be based on clinical assessment and family history. EA1 can be differentiated from EA2 to some degree on clinical grounds but also by EMG which may detect the myokymic discharges present in EA1 patients (Rajakulendran S. *et al*, 2007, *Neurotherapeutics* 4(2): 258 - 266). However a lack of myokymia does not necessarily mean that the individual does not have EA1.
How will the test add to the management of the patient or alter clinical outcome?	Confirming the diagnosis at the molecular level has an important impact for the patient and their family. Firstly, it consolidates the diagnosis and allows for prognostic clarification for the patient themselves. Secondly, identification of mutations in the *KCNA1* gene has prognostic implications for other family members. Presentation can be either *de novo* or with a clear family history. Mutation analysis will confirm diagnosis, allow for assessment of mosaicism and therefore more accurate recurrence risk. Predictive testing will be made available where appropriate. Thirdly, there are therapeutic implications with regards to the use of medication such as acetazolamide in treating the symptoms.
What impact will this test have on the NHS i.e. by removing the need for alternative management and/or investigations for this clinical population?	Molecular confirmation of the diagnosis stops the need to further investigate the patient in an attempt to reach a diagnosis, an often very costly process (MRI brain scan is usually normal in these patients, but often done as part of diagnostic workup)
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	No alternative means of diagnosis is available. Clinical diagnosis is generally based on phenotype, but there are a number of different diseases of the vestibular system that may be characterised by episodic “dizziness” and impaired balance. This is why genetic characterisation consolidates the correct diagnosis.
Are there specific ethical, legal or social issues with this test?	No

Please complete the referral pathway diagram on the following page and the testing criteria form.

Referral Pathway Template –

NOTE: Please use this page as a template. Please expand the test boxes manually as needed.

TARGET POPULATION
(Description)
Individuals with episodic ataxia with or without a family history of similar symptoms who are not likely to have EA2.

WHAT TYPE AND LEVEL OF PROFESSIONAL OR REFERRER DO YOU ACCEPT SAMPLES FROM?

We envisage that initially patients with symptoms of episodic ataxia will present to their GP, who will then refer to secondary care.

From here, the patient will be referred to an ataxia clinic / neurology services. If an ataxia clinic is not available the request may be initiated by the referring consultant neurologist / geneticist / paediatrician. If the patient is suspected of having EA1, genetic testing is requested after counselling and consent.

Parents of an affected child referred to a Clinical Geneticist for discussion regarding recurrence risk for future pregnancies and options for carrier testing. Testing would be carried out under instruction from a Clinical Geneticist following the counselling of the parents.

PLEASE PROVIDE DETAILS OF HOW REFERRALS WILL BE ASSESSED FOR APPROPRIATENESS?

Using *KCNA1* test criteria form

HOW MANY TESTS DO YOU EXPECT TO PERFORM ANNUALLY?

Up to 50

UKGTN Testing criteria:

Name of Disease(s): EPISODIC ATAXIA, TYPE 1; EA1 (160120)

Name of gene(s):
potassium voltage-gated channel, shaker-related subfamily, member 1 (episodic ataxia with myokymia); KCAN1 (176260)

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 Neuropaediatricians /Paediatric Neurologists	
Clinical Geneticists	
Consultant Neurologists	

Minimum criteria required for testing to be appropriate as stated in the Gene Dossier:

Criteria	Tick if this patient meets criteria
Episodic ataxia lasting seconds –minutes **AND TWO OF:** • Myokymia on EMG • a dominant family history • responsive to acetazolamide or linked to 12p13	
Individuals requiring carrier/predictive testing with a family history of EA1 where a KCNA1 mutation has been identified in affected relatives	
Affected members of families where the episodic ataxia has been shown to be linked to 12p13.	

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.