NHS
UK Genetic Testing Network

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

Test – Disease – Population Triad

Disease – name	LUBS X-LINKED MENTAL RETARDATION SYNDROME; MRXSL
OMIM number for disease	#300260
Disease – alternative names please provide any alternative names you wish listed	MECP2 duplication syndrome Mental retardation, X-linked, LUBS type Mental retardation, X-linked with recurrent respiratory infections LUBS XLMR syndrome
Disease – please provide a brief description of the disease characteristics	Males with duplications of Xq28 including MECP2 present with severe mental retardation, initial hypotonia, progressive spasticity, recurrent infections and absent speech. They may also have a dysmorphic appearance, undescended testicles, constipation and seizures. Childhood or teenage death is typical. Severity does not correlate with duplication size, however there is a suggestion that severity may correlate with copy number of the Xq28 region (i.e. triplicated males are more severely affected). Female carriers are generally asymptomatic and have favourable X-inactivation. Del Gaudio et al. Increased MECP2 gene copy number as the result of genomic duplication in neurodevelopmentally delayed males. *Genet Med* 2006:8(12):784–792 Meins M, Lehmann J, Gerresheim F, Herchenbach, J, et al. Submicroscopic duplication in Xq28 causes increased expression of the MECP2 gene in a boy with severe mental retardation and features of Rett syndrome. *J Med Genet* 2005;42:e12. Van Esch H, Bauters M, Ignatius J, Jansen M, et al. Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males. *Am J Hum Genet* 2005;77:442–453. Sanlaville D, Prieur, M, de Blois MC, Genevieve D, et al. Functional disomy of the Xq28 chromosome region. *Eur J Hum Genet* 2005;13:579–585. Friez MJ, Jones JR, Clarkson K, Lubs H, et al. Recurrent infections, hypotonia and mental retardation caused by duplication of MECP2 and adjacent region in Xq28. *Pediatrics* 2006, Nov 6;
Disease - mode of inheritance	X-linked

Gene – name(s)	Contiguous duplication of Xq28: Critical region – MECP2 and IRAK1 Flanking genes often also duplicated – SLC6A8, IDH3G, L1-CAM
OMIM number for gene(s)	MECP2 (*300005), IRAK1 (*300283)
Gene – alternative names please provide any alternative names you wish listed	
Gene – description(s) (including number of amplicons).	Contiguous gene duplications and triplications are detected in the Xq28 region encompassing the MECP2 and IRAK1 genes.
Mutational spectrum for which you test including details of known common mutations.	Duplications and occasionally triplications of MECP2 and IRAK1 often extending to flanking genes.
Technical Method (s)	MLPA of Xq28
Validation Process Note: please explain how this test has been validated for use in your laboratory	The primer and probe sequences within the MLPA kit (MRC Holland kit P015) have been checked to confirm that they bind to the correct regions within Xq28. The kit has been validated on Rett patient samples with known MECP2 deletions, and also normal controls.
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	Yes 47 reports issued 3 duplicated males 2 triplicated males 33 normal males 6 duplicated females 3 normal females (tested for carrier status)
For how long have you been providing this service?	18 months
Is there specialised local clinical/research expertise for this disease?	**Yes** | **Please provide details** Professor Angus Clark and Dr Hayley Archer have an extensive research record in Rett-like disorders
Are you testing for other genes/diseases closely allied to this one? Please give details	The laboratory is currently providing services for MECP2 (Rett syndrome) including deletion analysis, CDKL5 (infantile spasm syndrome) and ARX (ARX-related mental retardation). The laboratory has just initiated testing for FOXG1 (congenital Rett syndrome) and SLC9A6 (XL Angelman-like syndrome).
Your Activity If applicable - How many tests do you currently provide annually in your laboratory?	Index cases: 20 Family members where mutation is known: 6

Your Activity How many tests will you be able to provide annually in your laboratory if this gene dossier is approved and recommended for NHS funding?	Index cases: 20-50 Family members where mutation is known: 10
Based on experience how many tests will be required nationally (UK wide)? Please identify the information on which this is based	Index cases: 100 Family members where mutation is known: 20 Educated estimate based upon cohort of patients referred to Cardiff for specialist testing
National Activity **(England, Scotland, Wales & Northern Ireland)** If your laboratory is unable 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”.	No other laboratories currently known to be providing this analysis. However, other labs providing MECP2 analysis may set this up.

Epidemiology

Estimated prevalence of disease in the general UK population Please identify the information on which this is based	Not currently known. Duplications of Xq28 may be detected in a significant proportion of XLMR boys with recurrent infections.
Estimated gene frequency (Carrier frequency or allele frequency) Please identify the information on which this is based	Not currently known
Estimated penetrance Please identify the information on which this is based	100% for males (Females generally unaffected)
Target Population Description of the population to which this test will apply (i.e. description of the population as defined by the minimum criteria listed in the testing criteria)	Xq28 dosage studies are recommended in males with severe developmental delay, initial hypotonia, progressive spasticity, and absent speech, with a history of recurrent respiratory infections. Family members may require testing to confirm diagnosis and carrier status.
Estimated prevalence of disease in the target population	~15% 5/33 (Referrals for Xq28 duplication analysis - Cardiff) 2/122 (Referrals for *MECP2* deletion/duplication testing in neurodevelopmentally delayed males – Del Gaudio et al, 2006) 2/17 (Male patients selected for linkage to Xq28 – Friez et al, 2006).

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 for family members	√	
Risk Assessment – prenatal testing	√	

Test Characteristics

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. If more than one gene will be tested, please include your testing strategy and data on the expected proportions of positive results for each part of the process. Please illustrate this with a flow diagram.	Analytical sensitivity:- MLPA analysis of Xq28 for contiguous duplications is >99% sensitive, so this approach would detect essentially all duplications and triplications of this region. Analytical specificity:- >90% Partial duplications of MECP2 have been detected in rare cases. These mutations may not represent patients with this syndrome.
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)	Clinical sensitivity = 10-20% (of appropriately selected patients) Clinical specificity >95%
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).	Positive predictive value >95% (in males). Negative predictive value is low as many other genes (X-linked and otherwise) are known to contribute to a similar phenotype.

Clinical utility of test in target population (Please refer to Appendix A) Please provide a description of the clinical care pathway.	The majority of referrals will come from Clinical geneticists, Paediatric neurologists may also request this molecular analysis. Index patients should be male, and either sporadic cases or exhibiting X-linked inheritance. Patients should present with initial hypotonia and severe mental retardation. Clinical symptoms are also likely to include progressive spasticity, absent speech and recurrent infections. They may include a dysmorphic appearance, microcephaly, undescended testes, constipation and seizures. Unaffected family members may be tested for Xq28 duplications identified in index cases, to determine carrier status and therefore recurrence risks. If affected males are not available, analysis of Xq28 duplication could be considered for obligate female carriers.
How will the test add to the management of the patient or alter clinical outcome?	Detection of an Xq28 duplication or triplication allows confirmation of the cause of the phenotype in the patient and removes the need for further invasive tests. The parents and wider family can be advised of the likely clinical course and their risk of having another affected child. Pre-natal testing could be offered.
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?	Detection of an Xq28 duplication or triplication removes the need for extensive testing and clinical sessions for the patient to try and determine the cause of their phenotype.
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	It is not currently possible to diagnose this syndrome caused by Xq28 duplication / triplication by non-molecular methods. There is considerable overlap in phenotype with other severe types of mental retardation with or without associated hypotonia, spasticity, absent speech, and recurrent infections.
Please describe any specific ethical, legal or social issues with this particular test?	None anticipated.

Please complete the testing criteria form.

UKGTN Testing criteria

Name of Disease(s): LUBS X-LINKED MENTAL RETARDATION SYNDROME; MRXSL (300260)
Name of gene(s): Contiguous gene duplication / triplication of Xq28 (including MECP2 and IRAK1) methyl CpG binding protein 2 (Rett syndrome); MECP2 (300005) interleukin-1 receptor-associated kinase 1; IRAK1 (300283)

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 clinical geneticists	

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

Criteria	Tick if this patient meets criteria
ESSENTIAL CRITERIA	
Male	
Sporadic case or X-linked inheritance	
Severe mental retardation	
Initial hypotonia	
AND in infancy evidence of X-linked inheritance	
AND at least one MINOR CONGENITAL CRITERIA (apparent at birth)	
Dysmorphic appearance	
Microcephaly	
Undescended testicles	
And at least 2 of LATER MAJOR CRITERIA (These criteria are unlikely to be present at birth)	
Progressive spasticity	
Absent speech	
Recurrent infection	
OR relative at-risk in family with proven 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.