



Service Description

Spinal Muscular Atrophy (SMA)

1 Background

Spinal Muscular Atrophy (SMA) OMIM#253300

SMA is autosomal recessive, with a frequency of 1 in 10,000 (carrier frequency of approximately 1 in 38). Clinical features include: proximal muscle weakness, floppy baby, poor feeding, absent reflexes, arthrogryphosis, and fasciculation of tongue. SMA results from the degeneration of the anterior horn cells of the spinal cord. Approximately 95% of SMA patients have homozygous absence of exons 7 and 8 (or exon 7 only) of the Survival Motor Neuron 1 (*SMN1*) gene (i.e. they have no functional copies of the *SMN1* gene). The remainder of patients are compound heterozygotes for *SMN1* mutations, with a subtle mutation on one chromosome and a deletion or gene conversion on the other. The copy number of the adjacent *SMN2* gene has been shown to correlate with disease severity, however prediction of disease severity on this basis may not be accurate. SMA is clinically heterogeneous, classified into 4 types based on clinical severity:

SMA Types	Age of Onset	Prognosis
Type I (Werdnig-Hoffmann)	0 - 6 months	most severe, never sit, death in early infancy
Type II	< 2 years	never stand, death in early twenties
Type III (Kugelberg-Welander)	> 2 years	muscle wasting, survive into adulthood
Type IV	30-50 years	Least severe

2 Standard service

A Essential referral information

In addition to supplying standard patient identification and referral information (see Section I below), the following should be clearly indicated:

- Patient's symptoms.
- Any family history, including names, dates of birth, relationship, and genetic test results if available.

It is the responsibility of the referring clinician to ensure consent has been obtained for testing and storage.

B Samples required

Generally 5-10ml of EDTA blood (FBC bottle) is required. Sample identification policy is detailed at (see Section I below).

Blood specimens must be appropriately packaged (see Section I), and preferably sent by courier to arrive as soon as possible. Do not freeze prior or during postage.

Please note that extracted DNA is stored from patient's samples at the National Centre for Medical Genetics, and kept indefinitely unless a written request for its disposal is received from the patient or their parent/guardian.

Important note: The complete history of this document including its owner, author and revision date can be found on Q-Pulse

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National Centre for Medical Genetics

Dublin, Ireland

Division of Molecular Genetics

C Restrictions on testing

Carrier testing is only available via a Clinical Geneticist. Please refer your patient to Clinical Genetics if carrier testing for SMA is required.

Carrier testing is not offered for minors. This policy is consistent with international guidelines for genetic testing of children.

Prenatal or presymptomatic diagnosis is offered for families, only where an index case has previously been identified as either 1) homozygously deleted for the *SMN1* gene or 2) hemizyously deleted for the *SMN1* gene and with either a 2nd causative mutation identified OR a firm diagnosis of SMA, including a characteristic muscle biopsy.

D Tests offered

The SMA P021 MLPA assay is available in the National Centre for Medical Genetics, and is a quantitative test for *SMN1* gene copy number, <http://www.mrc-holland.com>.

Diagnostic: Molecular confirmation of a suggested clinical diagnosis.

Carrier testing: A direct test, to confirm carrier status or estimate the risk of being a carrier of the common *SMN1* mutation, is available at the NCMG. Referrals are accepted from individuals with a family history of SMA, and partners of such individuals. Carrier testing is only available via a Clinical Geneticist, and is not offered for minors.

Prenatal & Presymptomatic: Prenatal and presymptomatic diagnosis/exclusion (using MLPA, & additional linkage analysis if required) may be possible in families, but only where an index case has previously been identified as either 1) homozygously deleted for the *SMN1* gene or 2) hemizyously deleted for the *SMN1* gene, and with a 2nd causative mutation characterised OR a firm diagnosis of SMA, including a characteristic muscle biopsy. Prenatal testing must be arranged in advance with the laboratory, through a Clinical Genetics department if possible.

E Diagnostic Sensitivity of tests

The SMA MLPA assay is a quantitative test for *SMN1* gene copy number, and will not pick up subtle deletions, inversions or point mutations in *SMN1*- screening for such mutations can be arranged via external laboratories, where relevant. Diagnostic sensitivity of the MLPA assay is additionally influenced by the fact that approximately 4% of the *SMN1* alleles in the general population have two *SMN1* copies on a single chromosome.

Diagnostic: Homozygous deletion of the *SMN1* gene will be evident in approximately 95% of SMA Type I patients.

Carrier testing: Carrier status will be confirmed in approximately 96% of *SMN1* deletion carriers.

Prenatal & Presymptomatic: Providing linkage analysis is informative, prenatal & presymptomatic diagnosis should be possible, with an error rate due to recombination of less than 1%.

F Interpretation:

Results are given in the form of a written interpretative report to the referring clinician.

Diagnostic: Diagnosis is confirmed where a homozygous deletion of exons 7 and 8 (or exon 7 alone) of the *SMN1* gene is indicated. Hemizyous deletion of *SMN1* (i.e. 1 copy) reduces the likelihood that a patient is affected with SMA, but does not rule out a diagnosis of SMA.

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Over 99% of 5q13-linked SMA cases are excluded by an MLPA result which indicates 2 copies of *SMN1*.

Carrier testing: Detection of only one copy of the *SMN1* gene confirms deletion carrier status. In the absence of a family history, detection of two or three copies of the *SMN1* gene indicates a very low risk of carrying a deletion (<1%). Where there is a family history of SMA, detection of two copies of the *SMN1* gene indicates an intermediate risk of carrying a deletion (an estimate of this risk will be provided with individual reports), while detection of three copies of the *SMN1* gene indicates a very low risk of carrying a deletion (<1%).

Prenatal & Presymptomatic: For families in which an index case has been identified as homozygously deleted for the *SMN1* gene, prenatal/presymptomatic diagnosis is confirmed where a homozygous deletion of exons 7 and 8 (or exon 7 alone) of the *SMN1* gene is indicated. The absence of homozygous deletion of *SMN1* indicates a low risk of developing SMA (<1%). The clinical severity of SMA cannot be accurately predicted.

G Target reporting times:

As reporting times are constantly evolving, please refer to www.genetics.ie/molecular, or contact the molecular genetics laboratory, to receive up-to-date information on anticipated reporting times for your referral.

The following are current target reporting times for each category of test offered (information correct as of January 2010):

Diagnostic:	6 weeks Routine / 2 weeks Urgent (i.e. a neonate)
Carrier testing:	6 weeks Routine / 2 weeks Urgent (i.e. pregnancy)
Prenatal:	2 weeks CVS (4 weeks for amniotic fluid specimens)

- Please contact the laboratory if you have not received a report within a week of your patient being due back in clinic.
- Please note it is our policy not to issue verbal results.
- Request for copies of reports on the day that your patient is in clinic cannot normally be accommodated. We usually require 24 hours notice in which to fax a copy of a report.

H Further tests

The SMA MLPA assay is a quantitative test for *SMN1* gene copy number, and will not pick up subtle deletions, inversions or point mutations in *SMN1*- however, screening for such mutations can be arranged by us via external laboratories, where relevant (e.g. in the case of a suspected clinical diagnosis in the presence of a hemizygous deletion of *SMN1*). Please contact the laboratory for further information.

I Web Links to Related Documents

Standard referral information/NCMG request form
Sample/Patient identification policy
Packaging of specimens for transport

http://www.genetics.ie/pir/2006_NCMG_Referral_Form.pdf
<http://www.genetics.ie/pir/SampleIdentificationPolicyWeb.pdf>
http://www.genetics.ie/pir/sending_samples.pdf

Please note that hard copies of the above documents may be requested from:

Division of Molecular Genetics, National Centre for Medical Genetics, Our Lady's Children's Hospital, Crumlin, Dublin 12. Tel: 01 4096733; Fax: 01 4096971

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The NCMG Molecular Genetics laboratory participates in external QA schemes run by the UK NEQAS for Molecular Genetics, the European Molecular Genetics Quality Network (EMQN), and the Cystic Fibrosis European Network. Results of assessments are available for inspection upon request.

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