SW Thames Regional Genetics Laboratory
Sheet code: DISINFNOON.07

Lower Ground Floor,
Jenner Wing
St George's Hospital / SGUL
Cranmer Terrace,
London SW17 0RE
Tel: 020 8725 5332
Fax: 020 8725 0570
Web: www.southwestthamesgenetics.nhs.uk
Email: swtrgl@stgeorges.nhs.uk

St George's University Hospitals NHS
NHS Foundation Trust

SW Thames Regional Genetics Laboratory

CPA
Accredited Medical Laboratory
Reference No. 1905

UKGTN member

Noonan Spectrum Test – 23 gene panel for rasopathies

Introduction

The Noonan spectrum disorders are a group of clinically related syndromes resulting from pathogenic alteration of genes that form part of or regulate the Ras-MAPK signal transduction pathway (also known as **Rasopathies**). This term encompasses patients with a clinical diagnosis of Noonan syndrome, Noonan-like syndrome disorder with or without juvenile myelomonocytic leukaemia (NSLL), Noonan-like syndrome with loose anagen hair (NSLH), Cardio-facio-cutaneous syndrome (CFC), Costello syndrome, LEOPARD syndrome (multiple lentigines syndrome), Legius syndrome (Neurofibromatosis type 1-like syndrome) and Neurofibromatosis-Noonan syndrome (NFNS). Patients with these disorders have clinical features such as postnatal growth retardation; skeletal, ectodermal and haemotological anomalies; congenital heart defects including hypertrophic cardiomyopathy, and variable cognitive defects[1,2,3]. In addition the clinically distinct condition Capillary Malformation-Arteriovenous Malformation (CMAVM) is also caused by defects in a subset of these genes.

The genes included in the extended Noonan spectrum test are: *BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, SHOC2 (exon1 only), SOS1, SPRED1, A2ML1, RIT1, NF1, ARAF, KAT6B, MAP3K8, NSUN2, RASA1, RASA2, RRAS & SPRY1.* **All known pathogenic variants are targeted by the 23 gene panel.**

Referrals

• **Diagnostic testing**

- **NST pre-screen** (*PTPN11* exon 3 and 8) - individuals with a clinical diagnosis of a Noonan spectrum disorder or clinically relevant symptoms will have a prescreen (*PTPN11* exon 3 and 8) which detects ~15% of Noonan syndrome cases.
- **NST gene panel** –individuals can have the full 23 gene Noonan Spectrum Test either directly or following a pre-screen.

• **Confirmation testing** – confirmation of a pathogenic mutation that has been identified in a research laboratory

• **Familial/Predictive testing** – individuals (with or without symptoms) tested for a pathogenic mutation previously identified in an affected relative within the family or parents of an affected individual to assess whether a mutation has arisen *de novo* (~60%), confirming pathogenicity of a mutation and helping to predict recurrence risk.

• **Prenatal testing** – Diagnostic prenatal testing (*PTPN11* Exons 3&8) can be performed on CVS and amniocyte samples where abnormalities have been detected on scan. Noonan spectrum test may be requested for prenatal samples by discussion with the laboratory; however there may not be sufficient DNA from these samples for the complete analysis, and it is not always possible to get an urgent result. Predictive testing for familial mutations is available prenatally. Please contact the laboratory to discuss each case prior to sending prenatal samples (with maternal blood) to the laboratory.

Service offered

- Noonan Spectrum Pre-screen – *PTPN11* exon 3 and 8 - **£170**
- Noonan Spectrum test –targeted NGS and Sanger sequencing analysis of 23 genes - **£650**
- Confirmation and familial testing for any known mutation - **£170**

Technical

Noonan confirmation/ familial/ prenatal testing - samples tested by Sanger sequence analysis.
Diagnostic samples are tested using Next Generation Sequencing (Ion Personal Genome Machine® (PGM™) System).
Gene panel coverage including Sanger sequencing is shown overleaf. All exons with reported mutations are included in coverage.

Samples required
4-8mls venous blood in plastic EDTA bottles (1ml from neonates)
Minimum of 5µg DNA required for the Noonan Spectrum test referrals
Prenatals must be arranged in advance, through a Clinical Genetics department if possible.
Amniotic fluid or CV samples should be sent to Cytogenetics for dissecting and culturing, with instructions to forward the sample to the Regional Molecular Genetics laboratory for analysis
A completed DNA request form should accompany all samples (available by on our website at http://www.southwestthamesgenetics.nhs.uk/molecular_default.asp).
Patient details/GP name and address
To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, Address, postcode and ethnic origin), details of any relevant family history and full contact details for the referring clinician

SW Thames Regional Genetics Laboratory
Sheet code: DISINFNOON.07

Lower Ground Floor,
Jenner Wing
St George's Hospital / SGUL
Cranmer Terrace,
London SW17 0RE
Tel: 020 8725 5332
Fax: 020 8725 0570
Web: www.southwestthamesgenetics.nhs.uk
Email: swtrgl@stgeorges.nhs.uk

St George's University Hospitals NHS
NHS Foundation Trust

SW Thames Regional Genetics Laboratory

CPA Accredited Medical Laboratory Reference No. 1505

UKGTN member

Sanger sequencing is used to confirm any pathogenic mutations detected. Unclassified exonic variants and rare variants that occur +/- 11bp into the intron are reported but are not confirmed by Sanger sequencing.

Minimum Gene Panel Coverage Table (Including Sanger)

Gene	Reference Sequence	Minimum % ROI Covered by NGS (Depth >30) & Sanger Sequencing
A2ML1	NM_144670.3	97
ARAF	NM_001654.4	92
BRAF	NM_004333.4	99
CBL	NM_005188.3	100
HRAS	NM_005343.2	100
KAT6B	NM_012330.3	97
KRAS	NM_033360.3	100
MAP2K1	NM_002755.3	100
MAP2K2	NM_030662.3	95
MAP3K8	NM_005204.3	100
NF1	NM_001042492.2	99
NRAS	NM_002524.4	100
NSUN2	NM_017755.5	95
PTPN11	NM_002834.3	100
RAF1	NM_002880.3	100
RASA1	NM_002890.2	98
RASA2	NM_006506.2	90
RIT1	NM_001256821.1	100
RRAS	NM_006270.3	89
SHOC2	NM_007373.3	100
SOS1	NM_005633.3	96
SPRED1	NM_152594.2	100
SPRY1	NM_001258038.1	100
Overall Minimum Panel Coverage (%)		**97.7%**

Samples required
4-8mls venous blood in plastic EDTA bottles (1ml from neonates)
Minimum of 5µg DNA required for the Noonan Spectrum test referrals
Prenatals must be arranged in advance, through a Clinical Genetics department if possible.
Amniotic fluid or CV samples should be sent to Cytogenetics for dissecting and culturing, with instructions to forward the sample to the Regional Molecular Genetics laboratory for analysis
A completed DNA request form should accompany all samples (available by on our website at http://www.southwestthamesgenetics.nhs.uk/molecular_default.asp).
Patient details/GP name and address
To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, Address, postcode and ethnic origin), details of any relevant family history and full contact details for the referring clinician

SW Thames Regional Genetics Laboratory
Sheet code: DISINFNOON.07

Lower Ground Floor,
Jenner Wing
St George's Hospital / SGUL
Cranmer Terrace,
London SW17 0RE
Tel: 020 8725 5332
Fax: 020 8725 0570
Web: www.southwestthamesgenetics.nhs.uk
Email: swtrgl@stgeorges.nhs.uk

St George's University Hospitals NHS
NHS Foundation Trust

SW Thames Regional Genetics Laboratory

CPA
Accredited Medical Laboratory
Reference No. 1505

UKGTN member

References

1) Denayer E. et. al. (2008). J. Med. Genet. 45(11):695-703
2) Keren B. et al. (2004) J. Med. Genet. 41(11): e117
3) Niemeyer C. et. al. (2010) Nat. Gen. (2010) 42(9): 794-800
4) Aoki Y. et al. (2008) Hum. Mut. 0:1-15
5) Hart T. et. al. Am. J. Hum. Genet. 70:943-954
6) Bowen M. et. al. (2011). PLoS Genetics. 7(4): e1002050

Lab contacts

John Short 020 8725 0237 John.short@stgeorges.nhs.uk
Sandra Moore 020 8725 4729 Sandra.moore@stgeorges.nhs.uk

Samples required
4-8mls venous blood in plastic EDTA bottles (1ml from neonates)
Minimum of 5µg DNA required for the Noonan Spectrum test referrals
Prenatals must be arranged in advance, through a Clinical Genetics department if possible.
Amniotic fluid or CV samples should be sent to Cytogenetics for dissecting and culturing, with instructions to forward the sample to the Regional Molecular Genetics laboratory for analysis
A completed DNA request form should accompany all samples (available by on our website at http://www.southwestthamesgenetics.nhs.uk/molecular_default.asp).
Patient details/GP name and address
To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, Address, postcode and ethnic origin), details of any relevant family history and full contact details for the referring clinician