Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

Genetic Testing in Melanoma

Contact details:
Bristol Genetics Laboratory
Pathology Sciences
Southmead Hospital
Bristol, BS10 5NB
Enquiries: 0117 414 6168
FAX: 0117 414 6464

Head of Department:
Professor Rachel Butler, FRCPath
Consultant Clinical Scientist

Consultant Lead for Rare Disease:
Maggie Williams, FRCPath

Consultant Lead for Oncology:
Christopher Wragg, FRCPath

Service Lead:
ClaireFaulkner PhD
Claire.Faulkner@nbt.nhs.uk

Sample Required

Paraffin embedded tumour tissue

- **>20% tumour:** 5 x 10um sections in a clean universal
- **<20% tumour**: 10 x 5um slide mounted sections along with H&E with regions of >20% tumour highlighted

Samples should be accompanied by a FULLY completed Molecular Pathology request form (available from the laboratory or www.nbt.nhs.uk/genetics)

All samples should be labelled with patient name, date of birth and pathology block number

Consent and Storage:

All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

DNA is stored from **ALL** patients undergoing DNA testing, unless consent for this is specifically denied.

Stored material from all referrals may be retained for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

Clinical Background and Genetics

BRAF, *KIT, NRAS, GNA11 and GNAQ* mutation analysis is available at BGL for melanoma patients to guide targeted inhibitor therapy, clinical trial eligibility and diagnosis.

BRAF

37-50% of melanomas harbour a mutation in the *BRAF* gene, with the p.(Val600Glu) mutation (commonly known as V600E) accounting for 90% of *BRAF* variants in melanoma.

BRAF and MEK inhibitors are licensed and approved in the UK for patients with *BRAF* codon 600 mutation positive unresectable, advanced or metastatic melanoma[1]. Clinical trials have shown near 50% response rate and improved overall survival with vemurafenib (BRAF inhibitor) treatment compared to dacarbazine chemotherapy[2,3]. Furthermore, combinational therapy using trametinib (MEK inhibitor) plus dabrafenib (BRAF inhibitor) improved overall survival compared to dabrafenib plus placebo in a multicentre, double-blind, phase 3 randomised controlled trial[4]

KIT

Somatic *KIT* mutations have been found in 2–8% of all malignant melanoma. *KIT* mutations may be found in all melanoma subtypes but are the most common in acral melanomas (10–20%) and mucosal melanomas (15–20%)[5]. *KIT* mutated melanomas have been reported to respond to tyrosine kinase inhibitor (TKI) therapy such as imatinib[5].

NRAS

Somatic NRAS mutations are reported in 13-25% of malignant melanomas and are associated with resistance to BRAF inhibitors in *BRAF* mutated melanoma[5]. Clinical trials investigating MEK Inhibitor therapy in *NRAS* mutated melanoma are ongoing.

GNA11* and *GNAQ

34%-50% of primary uveal melanomas and 28%-63% of uveal melanoma metastases harbour a mutation in either the *GNA11* or *GNAQ* genes[5]. Testing can be used diagnostically to confirm an uveal primary in metastatic disease.

Service Offered

- Solid tumour Next Generation Sequencing (NGS) panel with analysis restricted to melanoma genes (Illumina TruSight Tumour 15 assay). Regions covered are: *BRAF* codons 581-605; *KIT* exons 8, 9, 10, 11, 13, 14, 17, 18; *NRAS* codons 1 to 22, codons 56 to 94, exon 4; *GNA11* codons 203 to 230; *GNAQ* codons 203 to 243.
- Urgent requests or requests for *BRAF* only are analysed by *BRAF* codon 600 pyrosequencing.
- These assays can detect a mutation at minimum 5% allele frequency in a background of wild type DNA.

Referrals

- Referrals are accepted from Consultant Oncologists, Dermatologists or Histopathologists.
- For sample requirements please refer to the information on the left.

Target Reporting Times

14 days maximum. Urgent requests: 3 days.

Quality

BGL participates in the *GENQA* scheme for this service.

References

1) NICE guidance: TA269, TA321, TA396
2) Flaherty KT et al *N Engl J Med.* 2010 Aug 26;363(9):809-19
3) Chapman PB et al *N Engl J Med.* 2011 Jun 30;364(26):2507-16.
4) Long G et al *Lancet* 2015 Aug 1;386(9992):444–451
5) Lovly C *et al* 2015. KIT in Melanoma. *My Cancer Genome* https://www.mycancergenome.org/content/disease/melanoma

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