Oxford Molecular Genetics Laboratory

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Familial Paraganglioma /Phaeochromocytoma

FH, MAX, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, VHL

INTRODUCTION

Phaeochromocytomas (PCC) are rare catecholamine secreting tumours that arise from chromaffin cells of the adrenal medulla. Extra-adrenal PCC are referred to as paragangliomas (PGL) and may be secretory or non-secretory (usually head/neck paragangliomas). PCC/PGL can occur in isolation or as part of a syndrome for example Von Hippel Lindau (VHL) and MEN2. There may or may not be a relevant family history.

Approx 30% of all PCC/PGL have a hereditary basis and are caused by mutation in one of a group of susceptibility genes, which includes; *VHL, RET, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, MAX, FH* and *NF1*[#]. Molecular analysis of *VHL, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, MAX, FH* and targeted analysis of *RET* would be expected to detect a mutation in;

- >44% all PGL (Jafri *et al* 2012 Clinical Endocrinology epub (Oct))
- 63-70% of all patients with a head/neck PGL (Baysal *et al*, 2002, Jafri *et al*, 2012 Clinical Endocrinology epub (Oct)
- >62% of patients with a diagnosis of PCC/PGL and a consistent family history (Jafri *et al*, 2012)
- 40-50% Malignant PCC (Maher *et al*, 2012)
- 24-28% of patients presenting with isolated PCC (Neumann et al, 2002 & Jafri *et al,* 2012, Clinical Endocrinology epub (Oct)

[#]*NF1* analysis is not undertaken in non-syndromic cases.

Isolated PCC presenting over the age of 45 years in patients with no relevant family history are most frequently sporadic.

It should be noted that individuals presenting with PCC but with germline mutations in the *VHL* and *RET* genes may be at risk of additional clinical symptoms reflective of the syndromes associated with the defective gene.

TESTING AND REFERRALS

Diagnostic screen: (Please complete PCC/PGL referral form)

- UK diagnostic referrals are accepted from Clinical Genetics, Endocrinology and Consultants from other relevant specialties. For NHSE referrals please refer to eligibility criteria (R223): https://www.england.nhs.uk/wp-content/uploads/2018/08/rare-and-inherited-disease-eligibility-criteria-march-19.pdf

Presymptomatic/predictive test for familial mutation:

- Relatives of individuals in whom a pathogenic mutation has been identified who are at risk of having inherited the mutation.
- Presymptomatic referrals should be referred through/in collaboration with Clinical Genetics departments

Prenatal:

- Prenatal testing is not usually requested
- Prenatal requests would only be accepted from clinical genetics and must be discussed with the laboratory and arranged in advance

STRATEGY & TECHNICAL INFORMATION

- Sequence and dosage analysis of *FH*, *MAX*, *RET* (exons 10&11), *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, *VHL* is undertaken by Next Generation Sequencing using the Custom Hereditary Cancer Solution (HCS) by Sophia Genetics along with the Sophia DDM analytical platform. Sequence analysis of *SDHA* is undertaken by Sanger sequencing (dosage analysis for *SDHA* is not undertaken).
- Regions of interest (ROI) are minimally defined as coding exons +/- 10bp and are guaranteed to be covered to 100% at >50x reads. Analytical sensitivity for single nucleotide substitutions is estimated to be >99%; analytical sensitivity for small insertions/deletions may be slightly lower.
- Putative pathogenic variants detected by NGS are confirmed by Sanger sequencing or Multiplex Ligation-dependent Probe Amplification (MLPA), as appropriate.
- Targeted testing (e.g. family testing) is undertaken by Sanger sequencing of the relevant exon or MLPA, as appropriate.

TARGET REPORTING TIMES (National Target)

Diagnostic screen:	42 calendar days
Predictive testing for known familial variant:	14 calendar days
Diagnostic testing for known familial variant:	42 calendar days
Prenatal testing:	3 calendar days

N.B. Details are correct for the date of printing only – last updated 03/07/2019