Oxford Molecular Genetics Laboratory

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Familial Paraganglioma /Phaeochromocytoma

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

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)

Isolated PCC presenting over the age of 45 years in patients with no relevant family history are most frequently sporadic. These individuals are tested for mutations in *SDHB* and *TMEM127* only, as mutations in the other genes usually present with earlier onset.

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: (Please complete PCC/PGL referral form)

- Clinically affected patients fulfilling 1 of the following criteria;
  - Presenting with PGL
  - PCC with family history PGL
  - Isolated PCC <45years of age
  - Malignant PCC >45yrs
  - Bilateral PCC/Multiple tumours
  - Isolated PCC >45yrs (limited screen only indicated)
  - PCC with other syndromic features – should be referred for specific syndrome testing.
- UK diagnostic referrals are accepted from Clinical Genetics, Endocrinology and Consultants from other relevant specialties

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

- Gene screening for most diagnostic referrals is undertaken by fluorescent Sanger sequencing of the coding region and exon/intron boundaries of the *VHL, SDHA, SDHB, SDHC, SDHD, SDHAF2, TMEM127, MAX* and *FH* genes plus targeted analysis of exons 10 and 11 of the *RET* gene. Dosage analysis by multiplex ligation-dependent probe amplification (MLPA) to look for gene rearrangements in *SDH* and *VHL* is also undertaken.
- Limited Screen: Patients referred with isolated phaeochromocytoma presenting >45years of age are screened for variants in *SDHB* and *TMEM127* only.
- When a pathogenic mutation has been identified in an individual, subsequent testing of family members (presymptomatic or diagnostic confirmation) involves testing for the familial mutation only

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

TARGET REPORTING TIMES

Diagnostic testing:	40 days
Carrier/Presymptomatic/Familial Mutation test:	10 days
Prenatal testing:	3 days

N.B. Details are correct for the date of printing only – last updated 05/05/2016