ARUP Consult

Paraganglioma/Pheochromocytoma Genetic Testing

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Recommendations for genetic testing for paraganglioma/pheochromocytoma
Genes in the boxes are most likely to account for the clinical picture described, but clinical presentation for hereditary paraganglioma/pheochromocytoma syndromes can be highly variable; a genetics consultation is recommended

- Clinical evaluation
- Directed testing for known familial variant (Familial Mutation, Targeted Sequencing)

Syndromic (personal or family history of below findings)

- Neurofibromas, optic glioma, Lisch nodules, café au lait spots → *NF1*
- Medullary thyroid cancer, parathyroid hyperplasia/adenoma → *RET* (MEN2)
- Renal cysts/carcinoma, hemangioblastoma, endolymphatic sac tumor → *VHL*

Single paraganglioma/ pheochromocytoma

Metastatic

- *SDHB*[a] → *SDHD, SDHC, MAX*[c]*, RET, TMEM127*[c]*, VHL*

Non-metastatic

- Extra-adrenal noradrenergic → *SDHB*[a]*, SDHD, SDHC, MAX*[c]*, VHL*
- Extra-adrenal dopaminergic → *SDHB*[a]*, SDHD, SDHC*
- Skull base and neck → *SDHB*[a]*, SDHD, SDHC*
- Pheochromocytoma (adrenal)
  - Noradrenergic → *VHL, SDHD, SDHB*[a]*, SDHC, MAX*[c]
  - Dopaminergic → *SDHD, SDHB*[a]*, SDHC*
  - Adrenergic → *RET, TMEM127*[c]*, MAX*[c]

SDHB immunohistochemistry

- Absent expression → *SDHB*[a]*, SDHC*[a]*, SDHD*[a]*, SDHA, SDHAF2*[c]

Multiple paragangliomas/ pheochromocytomas

- Malignant → *SDHB*[a]*, SDHD, SDHC, MAX*[c]*, TMEM127*[c]
- Head and/or neck → *SDHD*[a]*, SDHB, SDHC, SDHAF2*[c]*, TMEM127*[c]*, SDHA*
- Bilateral pheochromocytoma → *TMEM127*[c]
  - Increased norepinephrine → *VHL*
  - Increased epinephrine → *RET*

Family history consistent with a parent-of-origin effect – predisposition to paraganglioma/pheochromocytoma only with paternal transmission

- *SDHD*[a]*, MAX*[b,c]*, SDHAF2*[b,c]

The following genes can be ordered as part of Cancer Panel, Hereditary, Sequencing and Deletion/Duplication: *MAX*, *RET*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, *VHL*

Notes:
[a] Gene(s) most likely to account for phenotype
[b] Supporting literature is limited
[c] Rare

References:
- Fishbein L, et al. Inherited mutations in pheochromocytoma and paraganglioma: why all patients should be offered genetic testing. Ann Surg Oncol. 2013 May;20(5):1444-50.
- Lenders JW, et al; Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014 Jun;99(6):1915-42.
- Mannelli M et al. Clinically guided genetic screening in a large cohort of Italian Patients with pheochromocytomas and/or functional or nonfunctional paragangliomas. J Clin Endocrinol Metab 2009 May;94(5):1541-7.

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