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MAX **Mutations**

MAX-Associated Tumor Risks

Mutations in the *MAX* gene are primarily associated with increased risks for neuroendocrine tumors called paragangliomas (PGL) and pheochromocytomas (PCC). While many of these tumors are not cancerous, there is a risk for malignant transformation or other complications such as high blood pressure or stroke, so early detection is important.[2, 3]

MAX gene mutations are a rare cause of hereditary paragangliomas and pheochromocytomas, and the information outlined below may evolve as we learn more information about this gene. While data is still limited, the median age of onset of disease in *MAX* mutation carriers is 34 years. PCCs are the most common tumors observed in people with a *MAX* mutation and often present bilaterally or multifocally. Data suggest that these PCCs have a 10-25% change to become malignant. [6, 8, 9]. While they appear to be uncommon, PGLs of the head/neck and thorax/abdomen have also been reported. Studies of individuals with a mutation in the *MAX* gene have suggested a parent-of-origin effect: individuals only present with PGLs/PCCs when the mutation is inherited paternally (maternally imprinted). However, the number of reported cases of patients with a mutation in the *MAX* gene remains too small to conclusively say if this type of inheritance holds true for all individuals with a *MAX* mutation. [6-8] [6].

MAX-Associated Tumor Risks

Paraganglioma (PGL): Paragangliomas arise from neuroendocrine tissues symmetrically distributed along the paravertebral axis from their predominant location at the base of the skull and neck to the pelvis.[10]

- **Head and Neck PGL**: the parasympathetic-associated paragangliomas are generally located in the areas surrounding the carotid body, vagus nerve, and jugulotympanic region.[10, 11] Paragangliomas in these sites are usually nonfunctioning, although 5% may hypersecrete catecholamines. Carotid body paragangliomas classically present as asymptomatic, enlarging lateral neck masses and affected individuals may experience cranial nerve and sympathetic chain compression. Vagal paragangliomas present similarly to carotid body paragangliomas and affected individuals may experience dysphonia, hoarseness, pain or cough. Jugulotympanic paragangliomas can present with tinnitus or hearing loss and otoscopic examination may reveal blue-colored masses behind the tympanic membrane.[12]
- **Thoracic, Abdominal, and Pelvic PGL**: intra-abdominal and thoracic sympathetic-associated paragangliomas are generally functionally active with excess catecholamine production; however, 10% are biochemically silent.[10] Paragangliomas in these sites often present with symptoms associated with catecholamine hypersecretion, including elevations in blood pressure and pulse, headaches, palpitations, excessive sweating, and anxiety.[13, 14]

Pheochromocytoma (PCC): These are catecholamine-secreting paragangliomas confined to the adrenal medulla and are also known as adrenal chromaffin tumors.[10] As with extra-adrenal sympathetic paragangliomas, pheochromocytomas often present with symptoms associated with catecholamine hypersecretion, including elevations in blood pressure and pulse, headaches, palpitations, excessive sweating, and anxiety.[10, 11]

Other Risks: It is currently unknown if *MAX* mutations are associated with any other tumors or cancers. Further studies are needed to clarify what, if any, additional tumors may be associated with *MAX*.

MAX Screening and Management Recommendations

It is suggested that individuals with hereditary paraganglioma-pheochromocytoma syndrome have regular clinical monitoring by a physician or medical team with expertise in the treatment of hereditary PGL/PCC syndromes. A consultation with an endocrine surgeon, endocrinologist, and otolaryngologist is also recommended to establish an individualized care plan.

The Endocrine Society has published Pheochromocytoma and Paraganglioma Clinical Practice Guidelines.[15] Recommended screening is outlined below. In general, imaging modalities should be at the discretion of the managing provider due to conflicting data regarding the utility and efficacy of the various options.
Per the AACR Pediatric Oncology Series, routine screening should begin between the ages of 6 to 8 years.[18]

	***MAX* Surveillance Recommendations**	**Frequency**
Physical Exam	• Physical exam (including blood pressure and evaluation for arrhythmia and/or palpable abdominal masses)	Annually (at minimum)
Biochemical Screening for PGL/PCC	• 24 hour urine fractionated metanephrines and catecholamines and/or plasma free fractionated metanephrines ○ Follow-up imaging by CT, MRI, I-MIBG, or FDG-PET if levels become elevated or if the original tumor had minimal or no catecholamine/fractionated metanephrine excess • Plasma methoxytyramine	Annually
Imaging for PGL/PCC	• MRI/CT of skull base and neck, abdomen, thorax, and pelvis ○ Unless contraindicated, CT is generally recommended over MRI as a first-choice imaging modality due to its spatial resolution for the thorax, abdomen, and pelvis.	Every 2-4 years
	• Periodic 123I-MIBG (metaiodobenzylguanidine) scintigraphy may detect paragangliomas or metastatic disease that are not detected with MRI or CT	Every 2–4 years
Renal Cancer Screening	• Screening tests for renal cancer can include urinalysis (urine test) to screen for small amounts of blood in the urine or imaging tests (ultrasound, CT, MRI)	Consider at clinician discretion

Treatment: The management of tumors in individuals with hereditary PGL/PCC syndromes resembles management of sporadic tumors.[15]

Perioperative Medical Management: Individuals should undergo appropriate perioperative medical management including preoperative blockade of hormonally active tumors to prevent perioperative cardiovascular complication.[15]

Pregnancy Management: Evaluation for PGL/PCC should be performed prior to achieving pregnancy. However, after a diagnosis of PGL/PCC in pregnancy, it is important that delivery be in a tertiary hospital with an experienced obstetric, anesthetic, and endocrine service as well as a neonatal intensive unit.[17]

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *MAX* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- It has been suggested that *MAX* mutations are associated with paternal inheritance (maternal imprinting) and only increase the risk for tumor development if inherited from the father.[6, 8] This is called paternal transmission. Though paternal transmission in *MAX* mutations has been suggested, the number of reported cases at this time remains too small to conclusively say if this type of inheritance holds true for all individuals with *MAX* mutations. All at-risk relatives of an individual with a *MAX* mutation are recommended to have genetic counseling to discuss their risks.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

1. Dahia, P.L., *Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity.* Nat Rev Cancer, 2014. **14**(2): p. 108-19.
2. Barone, G., et al., *New strategies in neuroblastoma: Therapeutic targeting of MYCN and ALK.* Clin Cancer Res, 2013. **19**(21): p. 5814-21.
3. Grandori, C., et al., *The Myc/Max/Mad network and the transcriptional control of cell behavior.* Annu Rev Cell Dev Biol, 2000. **16**: p. 653-99.
4. Fishbein, L., et al., *Inherited mutations in pheochromocytoma and paraganglioma: why all patients should be offered genetic testing.* Ann Surg Oncol, 2013. **20**(5): p. 1444-50.
5. Neumann, H.P., et al., *Clinical predictors for germline mutations in head and neck paraganglioma patients: cost reduction strategy in genetic diagnostic process as fall-out.* Cancer Res, 2009. **69**(8): p. 3650-6.
6. Burnichon, N., et al., *MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma.* Clin Cancer Res, 2012. **18**(10): p. 2828-37.
7. Korpershoek, E., et al., *Complex MAX Rearrangement in a Family With Malignant Pheochromocytoma, Renal Oncocytoma, and Erythrocytosis.* J Clin Endocrinol Metab, 2016. **101**(2): p. 453-60.
8. Comino-Mendez, I., et al., *Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma.* Nat Genet, 2011. **43**(7): p. 663-7.
9. Welander, J., P. Soderkvist, and O. Gimm, *Genetics and clinical characteristics of hereditary pheochromocytomas and paragangliomas.* Endocr Relat Cancer, 2011. **18**(6): p. R253-76.
10. DeLellis, R.A., *Pathology and genetics of tumours of endocrine organs*. World Health Organization classification of tumours. 2004, Lyon: IARC Press. 320 p.
11. Lee, K.Y., et al., *Extraadrenal paragangliomas of the body: imaging features.* AJR Am J Roentgenol, 2006. **187**(2): p. 492-504.
12. Gujrathi, C.S. and P.J. Donald, *Current trends in the diagnosis and management of head and neck paragangliomas.* Curr Opin Otolaryngol Head Neck Surg, 2005. **13**(6): p. 339-42.
13. Young, W.F., Jr., *Paragangliomas: clinical overview.* Ann N Y Acad Sci, 2006. **1073**: p. 21-9.
14. Lenders, J.W., et al., *Phaeochromocytoma.* Lancet, 2005. **366**(9486): p. 665-75.
15. Lenders, J.W., et al., *Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline.* J Clin Endocrinol Metab, 2014. **99**(6): p. 1915-42.

16. Kirmani, S. and W.F. Young, *Hereditary Paraganglioma-Pheochromocytoma Syndromes*, in *GeneReviews(R)*, R.A. Pagon, et al., Editors. 2014: Seattle (WA).
17. Wing LA, Conaglen JV, Meyer-Rochow GY, Elston MS. Paraganglioma in Pregnancy: A Case Series and Review of the Literature. *The Journal of clinical endocrinology and metabolism.* 2015;100(8):3202-3209.

18. Rednam SP, Erez A, Druker H, et al. Von Hippel-Lindau and Hereditary Pheochromocytoma/Paraganglioma Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhood. *Clinical cancer 18. research : an official journal of the American Association for Cancer Research.* 2017;23(12):e68-e75.