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**Von Hippel-Lindau (VHL)**

Von Hippel-Lindau disease, or VHL, is cause by mutations in the *VHL* gene. Individuals with VHL, may develop multiple tumors in various parts of their body. Many of the tumors associated with VHL are vascular and many are not cancerous. However, these tumors can cause other health problems. The types of tumors associated with VHL are reviewed below.

- **Renal Tumors:** VHL is associated with renal cancer and renal cysts. Approximately 25-70% of individuals with VHL will develop renal cancer in their lifetime.[5] Renal cancers are typically treated surgically. Tumors less than 3 cm in size are typically monitored closely. Depending on the size and location of the tumor, nephron-sparing or partial nephrectomy may be possible in individuals with VHL.[4]

- **Hemangioblastoma in the Central Nervous System:** Individuals with VHL have an increased risk to develop vessel rich tumors of the brain (35-79%[8] risk) and spine (7-53%[8] risk). These are called hemangioblastomas, and can lead to headaches, vomiting, dizziness, and sometimes difficulty walking.

- **Hemangioblastoma in the Retina:** Individuals with VHL have a 25-60% risk for retinal hemangioblastomas, which are non-cancerous tumors in the eye. They often may not have symptoms but can occasionally cause vision loss.[3] Treatment of retinal hemangiomas varies based on tumor location and size.

- **Endolymphatic Sac Tumors (ELSTs):** Individuals with VHL have a 15% risk for endolymphatic sac tumors (ELSTs), which usually are benign tumors that form in the endolymphatic sac behind the inner ear. They can be associated with hearing loss.

- **Pheochromocytomas:** Individuals with VHL are at increased risk for benign tumors in the adrenal gland (called pheochromocytomas), which may cause high blood pressure. Treatment of pheochromocytomas in individuals with VHL is similar to that of sporadic pheochromocytomas. Partial adrenalectomy may be considered in VHL patients.[1]

- **Pancreatic Lesions:** Individuals with VHL have increased risk for pancreatic lesions: cysts, cystadenomas (serous microcystic adenomas) and islet cell tumors (pancreatic neuroendocrine tumor). Pancreatic cysts do not typically require treatments. Pancreatic neuroendocrine tumors may require surgical treatment if the tumor is larger than 3 cm, grows rapidly, or if the patient has a VHL mutation in exon 3.[2]

- **Cystadenomas:** Males with VHL are at risk to develop benign cystadenomas of the epididymis. Cystadenomas do not interfere with sexual function. They can be removed; however, removal is associated with a risk of sterility. Occasionally, depending on their position, cytadenomas themselves may block the delivery of sperm and cause infertility. Women with VHL may develop cystadenomas of the broad ligament near the fallopian tube.

Several organizations have proposed surveillance guidelines for individuals with VHL including the VHL Alliance and the American Association for Cancer Research (AACR)[6,7]. The VHL Alliance Active Surveillance guidelines are summarized below.

**VHL Suggested Active Surveillance Guidelines: [6]**

**Ages 1-4**

- *Annually*
    - Eye/retinal examination with indirect ophthalmoscope by an ophthalmologist skilled in diagnosis and management of retinal disease, especially for children known to carry the VHL mutation.
    - Pediatrician to look for signs of neurological disturbance, nystagmus, strabismus, white pupil, and abnormalities in blood pressure, vision, or hearing.

**Ages 5-15**

- *Annually*
    - Physical examination and neurological assessment by pediatrician informed about VHL, with particular attention to blood pressure (taken while lying down and standing), hearing impairment, neurological disturbance, nystagmus, strabismus, white pupil, and other signs indicating retinal problems.
    - Dilated eye/retinal examination with indirect ophthalmoscope by ophthalmologist informed about VHL.
    - Test for fractionated metanephrines, especially normetanephrine in a "plasma free metanephrine" blood test or in a 24-hour urine test. Abdominal MRI or MIBG scan only if biochemical abnormalities found.
    - Abdominal ultrasonography annually from 8 years or earlier if indicated.
- *Every 2-3 Years*
    - Audiology assessment by an audiologist. Annually if any hearing loss, tinnitus, or vertigo is found
    - In the case of repeated ear infections, MRI with contrast of the internal auditory canal using thin slices, to check for a possible ELST

**Age 16+**

- *Annually*
    - Physical examination by physician informed about VHL.
    - Dilated eye/retinal examination with indirect ophthalmoscope by ophthalmologist informed about VHL.
    - Quality ultrasound and at least every other year when not pregnant, an MRI scan of abdomen with and without contrast to assess kidneys, pancreas, and adrenals.
    - Test for fractionated metanephrines, especially normetanephrine in "plasma free metanephrines" blood test or 24-hour urine test. Abdominal MRI or MIBG scan if biochemical abnormalities found.
- *Every 2-3 Years*
    - MRI scans should be ordered as no less than a 1.5T MRI with and without contrast of brain, cervical, thoracic, and lumbar spine, with thin cuts through the posterior fossa, and attention to inner ear/petrous temporal bone to rule out both ELST and hemangioblastomas of the neuraxis.
    - Audiology assessment by an audiologist.

**During Pregnancy (for women with VHL)**

- Regular retinal checkup to anticipate potentially more rapid progression of lesions.
- Test for pheochromocytoma early, mid, and again late pregnancy to ensure no active pheochromocytoma during pregnancy or especially labor and delivery.
- During the 4th month of pregnancy, MRI—without contrast—to check on any known lesions of the brain and spine.
- If known retinal, brain, or spinal lesions, consider C-section.

*Implications for Family Members/Reproductive Considerations*

- First-degree relatives (i.e., parents, siblings, and children) have a 50% risk to have the familial *VHL* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% risk to have the familial mutation.

- Rarely, individuals inherit two *VHL* mutations (one from each parent), which in some instances may be associated with familial erythrocytosis, type 2.
    - Familial erythrocytosis is characterized by the abnormally high production of red blood cells (erythrocytes), which can cause headaches, dizziness, nosebleeds, shortness of breath and predisposition to excessive clotting.
    - *VHL* genetic testing for the partner of an individual with a *VHL* mutation may be appropriate to clarify the risk of having a child with familial erythrocytosis.
- 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 cancer risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

**References**


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