Seattle Children's
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# Description of the VANseq subpanels offered at Seattle Children's Hospital

**Capillary Malformations:** *EPHB4, GNA11, GNAQ, RASA1*

Capillary malformation-arteriovenous malformation (CM-AVM) syndrome is associated with multiple small (1-2 cm diameter) capillary malformations and is due to loss of function mutations in *EPHB4* or *RASA1*. Approximately 20% of individuals have AVMs, which can be life-threatening. Other features (telangiectasias, lymphedema, non-immune hydrops) have been associated. *RASA1* and *EPHB4* mutations are also associated with Parkes-Weber syndrome.

Somatic activating mutations at codon 183 in the *GNAQ* gene cause isolated capillary malformations or Sturge Weber Syndrome. Somatic activating mutations at the same residue in *GNA11* cause capillary malformation with overgrowth.

**LM/VM/AVM - Lymphatic Malformations, Venous Malformations, Arteriovenous Malformations:** *ACVRL1, ARAF, BRAF, ELMO2, ENG, EPHB4, GDF2, GLMN, HRAS, KRAS, MAP2K1, MAP3K3, NRAS, PIK3CA, PIK3R1, PTEN, RASA1, TEK (TIE2)*

Most individuals with isolated lymphatic, venous, or arteriovenous malformations possess somatic, activating mutations in genes associated with cell growth and division. For many of these conditions, sequencing of affected, lesional tissue is required for mutation detection, and coordination with pathology is required. Although there are strong gene-phenotype correlations within this group, there is increasing recognition of phenotypic expansion and overlap. The most commonly mutated gene in this group of conditions is *PIK3CA*.

- ~80% of isolated lymphatic malformations have pathogenic, tissue restricted variant in *PIK3CA.*
- Most venous malformations have activating mutations in *TEK* (*TIE2*). *TEK* mutations can be isolated and somatic or multifocal, inherited in a dominant fashion.
- Activating, somatic mutations in *MAP2K1* are primarily associated with isolated extracranial AVMs. Activating, somatic mutations in *KRAS* are primarily associated with isolated intracranial AVMs.

Many of the mutations associated with this group of vascular malformations lead to hyperactivation of PI3K-mTOR and RAS-MAPK pathways. Increasingly **specific pharmacologic inhibitors of components of this pathway are becoming available** (*mTOR* inhibitors, *MEK* inhibitors, *PIK3CA* inhibitors, *BRAF* inhibitors)

**Lymphedema:** *ANGPT2, ARAF, BRAF, CCBE1, CELSR1, DCHS1, EPHB4, FAT4, FLT4, FOXC2, GATA2, GJC2, HGF, HRAS, KIF11, KRAS, MAP2K1, MDFIC, MET, NRAS, PIEZO1, PTPN14, RASA1, SOX18, VEGFC*

Primary lymphedema is clinically and genetically heterogeneous, with pathogenic variants in >20 genes identified to date. Autosomal recessive, autosomal dominant, *de novo* constitutional, and somatic mosaic inheritance patterns have all been described. Many genetic causes of primary lymphedema are best classified by their additional, syndromic features (e.g immunodeficiency and myelodysplasia seen in *GATA2* related Emberger syndrome, or distichiasis seen in *FOXC2* related disorder)

**Vascular Tumor:** *BRAF, CTNNB1, GNA11, GNA14, GNAQ, HRAS, IDH1, IDH2, KRAS, NRAS*

Vascular tumors are distinguished from vascular malformations by the presence of increased endothelial cell proliferation. The most common vascular tumor, by far, is the infantile hemangioma (IH), which has no known genetic cause. Other vascular tumors, which are treated quite differently from infantile hemangiomas, include congenital hemangiomas, spindle cell hemangiomas (SCH), tufted angiomas (TA), kaposiform hemangioendothelioma (KHE), and juvenile nasopharyngeal angiofibromas (JNA). In combination with histopathological examination, genetic testing can help distinguish these vascular tumors, which vary greatly in their prognosis and treatment.

- Congenital hemangiomas (both rapidly involuting and non-involuting) have been associated with somatic activating *GNAQ* and *GNA11* mutations
- TA and KHE are more aggressive vascular tumors that can be associated with Kasabach-Merritt phenomenon (a thrombocytopenic consumptive coagulopathy. Somatic activating *GNA14* mutations are causative.
- Somatic activating mutations in *IDH1* (p.R132) and *IDH2* (p.R140 and R172) are associated with SCH, either in isolation or in the setting of multiple enchondromas (Maffucci syndrome)
- JNA is a tumor seen more commonly in adolescent males. It is associated with somatic activating *CTNNB1* mutations.
- Activating, somatic mutations in *BRAF, HRAS, KRAS, NRAS* can be associated with a wide variety of vascular and non-vascular cutanenous tumors, such as pyogenic granuloma, wooly hair nevus, melanocytic nevi, and sebaceous nevus.