ALBERTA PRECISION LABORATORIES
Leaders in Laboratory Medicine

Inherited Vascular Disorder Panels: Information for Ordering Providers

Inherited vascular disorders are a heterogenous group of conditions that affect blood vessel development and function. Many of these disorders increase an individual's risk to develop vascular anomalies, which can be classified as either vascular tumours or vascular malformations. Vascular malformations can be further defined based on the type of blood vessel that is affected and the speed of blood flow: venous, capillary, and lymphatic malformations are slow-flow lesions whereas arteriovenous malformations and arteriovenous fistulas are high-flow lesions.[1]

The panels listed below include genes related to vascular malformations, pulmonary arterial hypertension, and/or cerebral small vessel disease. Associated clinical features or genetic conditions are listed for each gene and the inheritance pattern for each condition (AD – autosomal dominant, AR – autosomal recessive, XL – X-linked).

Ordering Privileges

Please refer to the APL Test Directory (http://ahsweb.ca/lab/apl-td-lab-test-directory) for specific ordering restrictions for each panel.

Cerebral Cavernous Malformation Panel

Cerebral cavernous malformations (CCMs) are comprised of enlarged capillaries in the brain and spinal cord that have abnormal shape and structure. The blood vessel walls are abnormally thin and lack intervening brain parenchyma. CCMs are typically identified between the second and fifth decades of life when individuals present with associated neurological symptoms including seizures, focal neurologic deficits, nonspecific headaches, and cerebral hemorrhage. Familial CCM should be suspected in an individual with multiple CCMs, or one CCM and at least one other family member with one or more CCMs. Cutaneous vascular lesions and retinal vascular lesions may also be identified in people with familial CCM. Many individuals with familial CCM never experience any symptoms, and studies have demonstrated genotype-phenotype correlations with this condition. Individuals with CCM-1 typically have a milder clinical course, whereas individuals with CCM-3 are more likely to present with severe symptoms such as brain tumors or hemorrhage, with an earlier age of symptom onset.[2,3]

Genes	Associated clinical features or genetic conditions[6]	Inheritance
CCM2	Cerebral cavernous malformations-2	AD
KRIT1	Cerebral cavernous malformations-1	AD
PDCD10	Cerebral cavernous malformations-3	AD
RASA1	Capillary malformation - arterial venous malformation; Parkes Weber syndrome	AD

Hereditary Hemorrhagic Telangiectasia/Arteriovenous Malformation Panel

Arteriovenous malformations (AVMs) can occur in individuals with Hereditary Hemorrhagic Telangiectasia (HHT) and Capillary Malformation-Arterial Venous Malformation (CM-AVM) syndrome. HHT is characterized by AVMs, mucocutaneous telangiectasias, and epistaxis. AVMs can present in the lungs, brain, liver, spine, gastrointestinal tract or pancreas. Individuals with at least two of the features listed above, or one feature plus a family history of HHT should be suspected to have this condition. Molecular testing for HHT may help confirm a diagnosis if the clinical features are inconclusive. CM-AVM syndrome is characterized by small capillary malformations located on the face and limbs in addition to AVMs and/or arterial venous fistulas (AVFs) in the skin, muscle, bone, spine, and brain. Capillary malformations and micro-AVFs are also common features of Parkes Weber syndrome. These vascular malformations can result in abnormal bleeding, heart failure, and neurologic symptoms. [2, 3]

Genes	Associated clinical features or genetic conditions[6]	Inheritance
ACVRL1	Hereditary hemorrhagic telangiectasia type 2	AD
ENG	Hereditary hemorrhagic telangiectasia type 1	AD
GDF2	Hereditary hemorrhagic telangiectasia type 5	AD
RASA1	Capillary malformation - arterial venous malformation	AD
SMAD4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome; Myhre syndrome; Polyposis, juvenile intestinal	AD
TEK	Venous malformations, multiple cutaneous and mucosal	AD

Heritable Pulmonary Arterial Hypertension Panel

Pulmonary arterial hypertension (PAH) is characterized by obstruction of the pulmonary arteries which increases the resistance of blood flow to the lungs. To overcome this resistance, the right ventricle increases the blood pressure which results in hypertension and ultimately progressive heart failure. PAH is clinically defined as a mean pulmonary artery pressure of >25 mmHg at rest or >30 mmHg during exercise. [2] Initial symptoms of PAH may include dyspnea, fatigue, syncope, chest pain, palpitations, and leg edema. Heritable PAH encompasses individuals presenting with PAH where other known causes of pulmonary hypertension have been excluded, and a pathogenic variant is identified in a known gene or two or more family members are affected. Pathogenic variants in *BMPR2* account for most families who have a molecular diagnosis of heritable PAH. Less common genetic causes of heritable PAH include variants in *CAV1, KCNK3, and SMAD9.*[2] Individuals with HHT and CM-AVM syndrome can also present with PAH [2, 4]

Genes	Associated clinical features or genetic conditions[6]	Inheritance
ACVRL1	Hereditary hemorrhagic telangiectasia type 2	AD
BMPR2	Pulmonary hypertension, primary; Pulmonary venoocclusive disease	AD
CAV1	Lipodystrophy, familial partial, type 7; Pulmonary hypertension, primary, type 3	AD
ENG	Hereditary hemorrhagic telangiectasia type 1	AD
GDF2	Hereditary hemorrhagic telangiectasia type 5	AD
KCNK3	Pulmonary hypertension, primary, type 4	AD
RASA1	Capillary malformation - arterial venous malformation; Parkes Weber syndrome	AD
SMAD4	Juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome; Myhre syndrome; Polyposis, juvenile intestinal	AD
SMAD9	Pulmonary hypertension, primary, type 2	AD

Leukodystrophy and/or Porencephalopathy with Vascular Stroke Panel

Cerebral small vessel disease (SVD) affects the small arteries, arterioles, venules, and capillaries of the brain, as well as surrounding perivascular structures. Cerebral SVD is a leading cause of ischemic stroke, intracerebral hemorrhage, and vascular dementia worldwide. While cerebral SVD is typically due to a combination of genetic and environmental risk factors, several single-gene disorders causing cerebral SVD have been identified. Clinical features of these conditions include lacunar infarct, transient ischemic attack, intracerebral hemorrhage, progressive dementia, cognitive impairment, psychiatric disorders, and migraine. Neuroimaging studies typically identify cerebral white matter lesions, lacunes of presumed vascular origin, cerebral microbleeds, dilated perivascular spaces, and total cerebral atrophy.[2, 5, 7]

Genes	Associated clinical features or genetic conditions[6]	Inheritance
COL4A1	Angiopathy, hereditary, with nephropathy, aneurysms, and muscle cramps; Brain small vessel disease with or without ocular anomalies; Pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL)	AD
COL4A2	Brain small vessel disease	AD
HTRA1	CARASIL syndrome; CADASIL, type 2	AD/AR
NOTCH3	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); Lateral meningocele syndrome	AD
TREX1	Aicardi-Goutieres syndrome 1; Chilblain lupus; Vasculopathy, retinal, with cerebral leukodystrophy	AD/AR

When can I expect results?
Results may take up to 4 months.

How are results reported?
Results are sent to the ordering provider and available in Netcare and Connect Care.

Contact Information
Genetic Counsellors, Genetics & Genomics
Calgary: 403-955-3097

Requisition forms, contact information and other resources can be found at http://ahsweb.ca/lab/if-lab-genetics-and-genomics

References

1. ISSVA Classification of Vascular Anomalies ©2018 International Society for the Study of Vascular Anomalies Available at "issva.org/classification" Accessed July 29, 2020.
2. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020 [cited 2020 July]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/
3. National Library of Medicine (US). Genetics Home Reference [Internet]. Bethesda (MD): The Library; 1993-2018 [cited 2020 July]. Available from: https://ghr.nlm.nih.gov/
4. Wooderchak-Donahue, W. L., Johnson, P., McDonald, J., Blei, F., Berenstein, A., Sorscher, M., Mayer, J., Scheuerle, A. E., Lewis, T., Grimmer, J. F., Richter, G. T., Steeves, M. A., Lin, A. E., Stevenson, D. A., & Bayrak-Toydemir, P. (2018). Expanding the clinical and molecular findings in RASA1 capillary malformation-arteriovenous malformation. *European journal of human genetics : EJHG*, *26*(10), 1521–1536. https://doi.org/10.1038/s41431-018-0196-1
5. Choi J. C. (2015). Genetics of cerebral small vessel disease. *Journal of stroke*, *17*(1), 7–16. https://doi.org/10.5853/jos.2015.17.1.7
6. Online Mendelian Inheritance in Man, OMIM®. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), July 29, 2020. World Wide Web URL: https://omim.org/
7. Li, Q., Yang, Y., Reis, C., Tao, T., Li, W., Li, X., & Zhang, J. H. (2018). Cerebral Small Vessel Disease. *Cell transplantation*, *27*(12), 1711–1722. https://doi.org/10.1177/0963689718795148