RASA1

The RASA1 gene provides instructions for making a protein called p120-RasGAP. This protein helps regulate the RAS/MAPK signaling pathway, which transmits signals from outside the cell to the cell's nucleus. The RAS/MAPK signaling pathway helps direct several important cell functions, including the growth and division (proliferation) of cells, the process by which cells mature to carry out specific functions (differentiation), and cell movement. The p120-RasGAP protein is a negative regulator of the RAS/MAPK signaling pathway, which means it is involved in turning off these signals when they are not needed.

The exact role of p120-RasGAP is not fully understood. However, it appears to be essential for the normal development of the vascular system, which is the complex network of arteries, veins, and capillaries that carry blood to and from the heart.

RASA1-related disorders are characterized by the presence of multiple small (1-2 cm in diameter) capillary malformations mostly localized on the face and limbs. About 30% of affected individuals also have associated arteriovenous malformations (AVMs) and/or arteriovenous fistulas (AFVs), fast-flow vascular anomalies that typically arise in the skin, muscle, bone, spine, and brain; life-threatening complications of these lesions can include bleeding, congestive heart failure, and/or neurologic consequences. Symptoms from intracranial AVMs/AVFs appear to occur early in life. Several individuals have RASA1-related Parkes Weber syndrome (multiple micro-AVFs associated with a cutaneous capillary stain and excessive soft-tissue and skeletal growth of an affected limb). DIAGNOSIS/TESTING:

The diagnosis of a RASA1-related disorder is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in RASA1 identified by molecular genetic testing. MANAGEMENT:

Treatment of manifestations: For capillary malformations that are of cosmetic concern, referral to a dermatologist. For AVMs and AVFs, the risks and benefits of intervention (embolization vs surgery) must be considered, usually with input from a multidisciplinary team (e.g., specialists in interventional radiology, neurosurgery, surgery, cardiology, and dermatology). For cardiac overload, referral to a cardiologist. For hemihyperplasia and/or leg-length discrepancy, referral to an orthopedist. Lymphangiography to evaluate for lymphatic malformations may be considered; compression stockings for those with evidence of lymphedema. Surveillance: Repeat imaging studies if clinical signs/symptoms of AVMs/AVFs become evident. Evaluation of relatives at risk: Clarification of the genetic status of at-risk relatives is appropriate in order to allow early diagnosis and treatment of AVMs/AVFs to reduce/avoid secondary adverse outcomes. GENETIC COUNSELING:

RASA1-related disorders are inherited in an autosomal dominant manner. About 70% of affected individuals have an affected parent; about 30% have a de novo pathogenic variant. Each child of an individual with a RASA1-related disorder has a 50% chance of inheriting the pathogenic variant. Prenatal diagnosis for pregnancies at increased risk and preimplantation genetic diagnosis are possible if the RASA1 pathogenic variant has been identified in an affected family member [1)].

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Bayrak-Toydemir P, Stevenson D. RASA1-Related Disorders. 2011 Feb 22 [updated 2016 Oct 6]. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Ledbetter N, Mefford

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