Genetic Aspects of Vascular Malformations

4

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Introduction

The past several years have been an exciting period for vascular anomalies for a number of reasons:

1. An escalation in basic research has been instrumental in illuminating the etiology and pathogenesis of vascular anomalies by identifying cellular properties and putative regulatory pathways [1, 2] and detecting new genetic findings [3–9].
2. Refined radiologic techniques permit more precise evaluation [10–13].
3. The identification of new effective treatments, some of which were derived from in vitro and in vivo laboratory discoveries [14–16].

This chapter will focus on genetic mutations which have been identified in vascular malformations. Selected references are updated reviews when possible. Reference to the updated ISSVA classification is recommended (ISSVA classification of vascular anomalies ©2014 available at "issva.org/classification") as well as the manuscript explaining this classification [17]. Refer to Table 8.1.

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Mutations are either *germline* (in the case of familial vascular malformations) or *somatic*. Figure 4.1 illustrates the differences between the types of mutations in pictorial form. Germline mutations are autosomal recessive, autosomal dominant, or sex linked; however, other possibilities are de novo mutations, or mutations with variable expression and incomplete penetrance, with clinically unaffected family members carrying the mutation. Mutations are frequently but not exclusively activating or loss of function mutations.

Heritable (*genomic*, *germline*) *mutations*, which occur during meiosis, have been identified in affected family members with a variety of vascular malformations (Tables 4.1 and 4.2) including familial mucosal venous malformations (Tie2 activating mutation) [18], arteriovenous malformations with multifocal capillary malformations (CM-AVM, RASA1 gene) [19], glomuvenous malformations (glomulin) [20], hereditary hemorrhagic telangiectasia (HHT) (endoglin, Alk1, and others) [21], and cerebral cavernous malformations (CCMs) (KRIT1, MGC4607, PDCD10) [22], patients with PTEN hamartoma syndromes (Cowden's syndrome and Bannayan-Riley-Ruvalcaba syndrome), and patients with lymphatic malformations and vascular malformation syndromes with lymphatic malformations [23]. Additionally, several genetic mutations have been identified in familial lymphedema syndromes (VEGFR3/FLT4, VEGFD, FOXC2, *CCBE1*, SOX18, and others) [9]. For those

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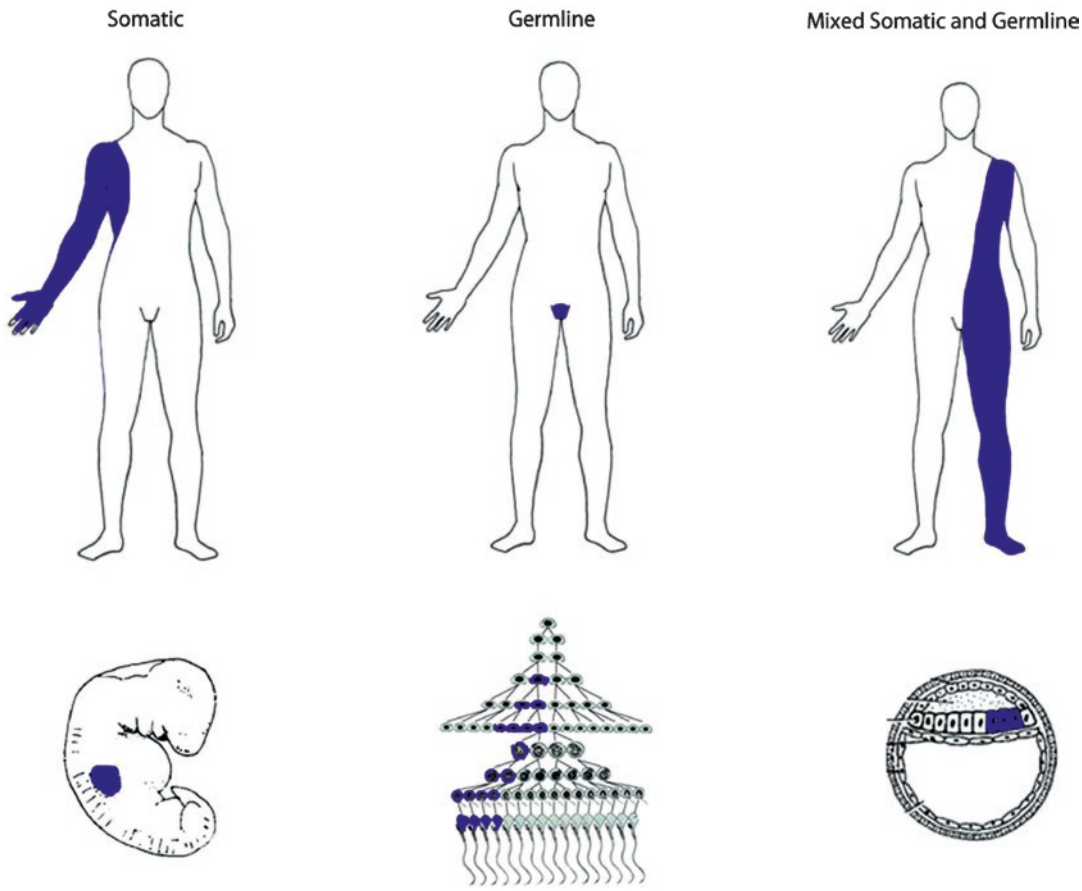

Fig. 4.1 Mosaicism and clinical genetics: This figure shows possible distributions of a mutation in adults with purely somatic, purely germline, or mixed somatic and germline patterns along the top row. The bottom figures demonstrate possible mutation patterns in the late embryo, during spermatogenesis, and in the early embryo (Copyright permission obtained. Spinner and Conlin [30])

disorders that have a defined heritable mutation, prenatal genetic testing may be possible, via amniocentesis, chorionic villus sample, or preimplantation genetic testing.

Mutations in heritable vascular anomalies syndromes are summarized in Table 4.2. The genetic basis of hereditary hemorrhagic telangiectasia was initially discovered in the late 1990s. Since then, genotype-phenotype correlations have been identified, and several causative genes have been found. However, most patients appear to have mutations in endoglin (type 1 HHT) or Alk1 (type 2 HHT) [21]. Familial venous malformations were found to be multifocal, affecting cutaneous and/or mucosal locations. A mutation in the angiopoietin receptor TIE2/TEK was found to be causative [3]. Patients with capillary malformation-arteriovenous malformation often present with symptoms associated with an arteriovenous malformation. Multiple small macular pink/brown cutaneous lesions (capillary malformations) of varying sizes evolve over time. A comprehensive family history may identify similarly affected asymptomatic family members, and genetic testing for the RASA1 mutation should be discussed [19]. As mentioned above, several lymphedema syndromes and familial lymphedema disorders have been characterized genetically, and at least one third of familial lymphedemas have been attributed to VEGF3

Table 4.1 Genetic mutations in overgrowth syndromes associated with vascular anomalies

Diagnosis	Clinical features	Mutation	Reference
CLOVES syndrome OMIM 612918	Congenital lipomatous overgrowth, vascular malformation, epidermal nevus, skeletal/spinal abnormalities	3q26.32 PIK3CA gene somatic mosaic activating mutations	Sapp et al. (2007), Alomari et al. (2009), Kurek et al. (2012) [32, 34, 35]
Proteus syndrome OMIM 176920	Asymmetric progressive, disproportionate overgrowth syndrome, hyperostosis, cerebriform connective tissue nevus, vascular malformation, cystic lung disease	AKT1 gene somatic mosaic activating mutations 14q32.33	Lindhurst et al. [31]
Megalencephaly-capillary malformation-polymicrogyria syndrome MCAP, M-CM OMIM 602501	Megalencephaly with brain malformation (polymicrogyria), prenatal overgrowth asymmetry, cutaneous vascular malformation, syndactyly ± polydactyly, connective tissue dysplasia	PIK3CA activating mutation 3q26.32	Mirzaa (2012), (2013) [36, 37]
Klippel-Trenaunay syndrome OMIM 149000	Capillary malformation, soft tissue overgrowth, vascular malformation	PIK3CA activating mutation 3q26.32	Luks et al. [23]
Parkes Weber syndrome OMIM 608355	Capillary malformation, arteriovenous malformation, ± soft tissue overgrowth	Somatic RASA1 5q14.3	Revencu et al. [38]
Capillary malformation-arteriovenous malformation OMIM 608354	Capillary malformation, soft tissue overgrowth, vascular malformation and arteriovenous fistula	Germline RASA1 activating mutation 5q14.3	Eerola et al. (2003), Boon (2005) [19, 39]
Sturge-Weber syndrome OMIM 185300	Facial capillary malformation (PWS), glaucoma, CNS leptomeningeal angiomatosis (encephalotrigeminal angiomatosis), bone ± soft tissue overgrowth	Somatic GNAQ 9q21	Shirley et al. [8]
PTEN hamartoma syndromes Bannayan-Riley-Ruvalcaba syndrome OMIM 153480 Cowden's syndrome OMIM 158350	Macrocephaly, vascular malformation, lipomas thyroid disorders, penile lentigines (BRRS), trichilemmomas, papillomatous	Germline PTEN 10q23.31	Eng (2001), Orloff et al. (2008), Pilarski et al. (2013), Nieuwenhuis et al. (2014), Tan et al. [40–43], [44]
Facial infiltrating lipomatosis	Unilateral facial soft tissue with skeletal overgrowth, premature dentition with macrodontia, hemimacroglossia, mucosal neuromas	Somatic PIK3CA activating mutation	Maclellan [45]
Maffucci syndrome OMIM 614569	Venous malformation, ± spindle cell hemangioma, + enchondromas	Somatic (isocitrate dehydrogenase 1 or 2), IDH1 IDH2	Amary et al. [46]
SOLAMEN	Segmental proportional overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus	PTEN 10q23.3 mosaic PTEN wild-type allelic loss	Caux et al. [47]

Table 4.2 Heritable vascular malformations

Diagnosis			Reference
Familial venous malformations OMIM 600195	Multifocal cutaneous or mucosal venous malformations	Angiopoietin receptor TIE2/TEK 9p21.2	Gallione et al. [3]
Capillary malformation-arteriovenous malformation, CM-AVM OMIM 608354	See Table 4.1	See Table 4.1	See Table 4.1
Cerebral cavernous malformations OMIM 116860	Single or multiple dilated capillaries in the brain (especially the forebrain), spinal cord, or elsewhere	Sporadic or inherited (AD, incomplete penetrance, variable expression) CCM1: 7q21–22 KRIT1 CCM2: 7p13–15 MGC4607 CCM3: 3q25.2–27 PDCD10	Cigoli et al. [25]
Hereditary hemorrhagic telangiectasia OMIM 187300, 600376, and others	Multifocal arteriovenous malformations	Genotype-phenotype correlation Most common types Type 1 Endoglin *(ENG)* 9q34.11 Type 2 Activin receptor-like kinase 1 (*ACVRL1*) 12q13.13	Review McDonald et al. [21]
Glomovenous malformations OMIM 13800	Non-mucosal venous malformation with glomus cells, may be tender, may be segmental	Autosomal dominant glomulin gene 1p22.1	[20]
PTEN hamartoma syndromes	See Table 4.1	See Table 4.1	See Table 4.1

pathway mutations [24]. Familial CNS cavernous malformations may be single or multiple and can occur in the brain or spinal cord. Several genes (on chromosome 7q and 3q) have been identified in affected families; however, the majority of mutations are associated with the KRIT1 gene (CCM1) [25].

Somatic mutations are post-zygotic mutations which occur after fertilization and only occur in the affected cells. Somatic have been identified in the affected tissue of patients with vascular malformations syndromes, as discussed below and listed in Table 4.1.

Happle [30] introduced the notion that certain genes survive by mosaic expression, since if expressed fully they would be incompatible with life. Several reviews expound upon genetic mosaicism in a multiplicity of disorders [26–30]. Relevant to vascular anomalies is the left panel in Fig. 4.2, somatic mosaicism, demonstrating the mutation occurring in the developing fetus. The earlier in gestation the mutation occurs, the more extensive the involvement. This is evident with the GNAQ mutation which was identified in non-syndromic cutaneous capillary malformations (port-wine stains) and in the cutaneous capillary malformations of patients with Sturge-Weber syndrome (where the mutation presumably occurred earlier in gestation, thus affecting more cell types) [8].

PIK3CA, AKT1, and GNAQ are heretofore the most commonly identified in those syndromic vascular malformations for which somatic mutations have been identified (Table 4.1). These diagnoses include Parkes Weber syndrome,

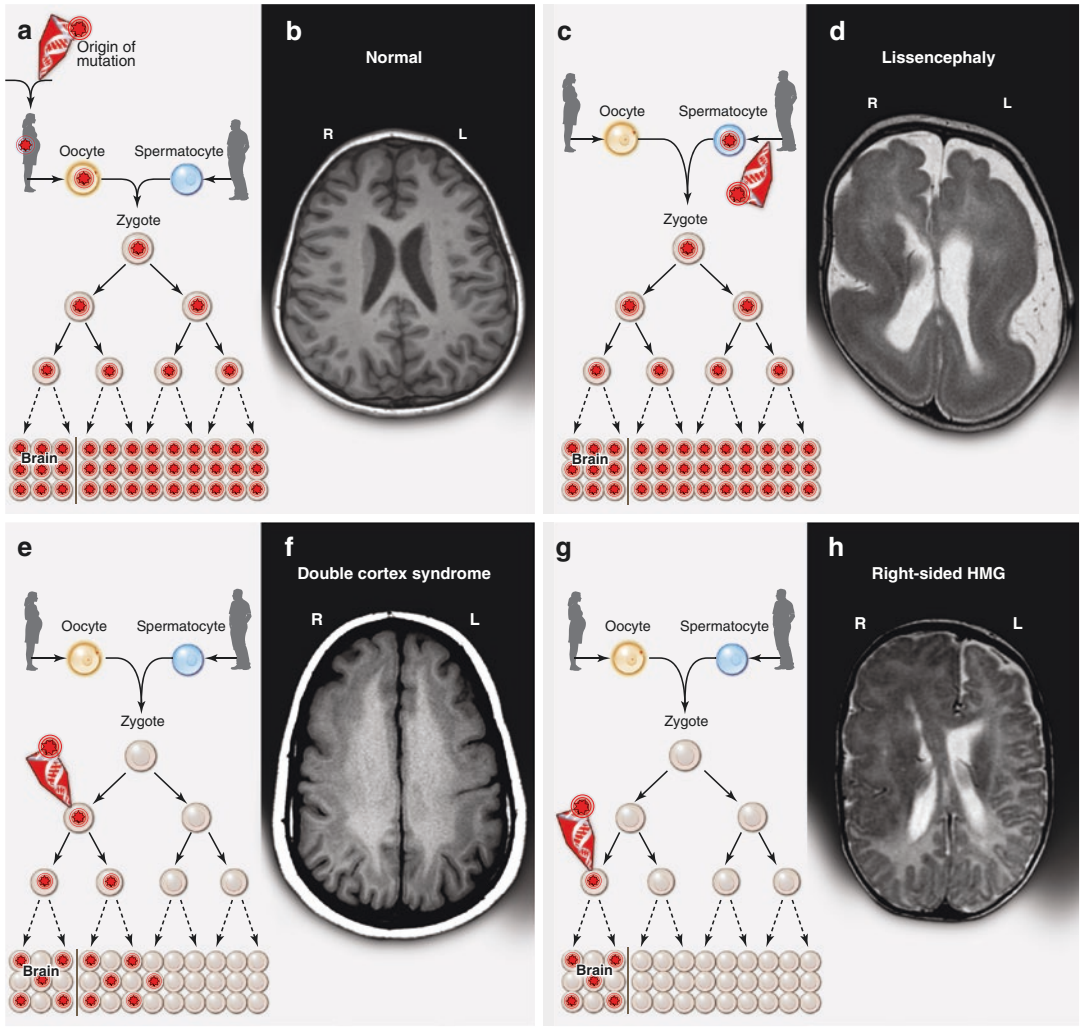

Fig. 4.2 Illustration of genomic mutations (A and C) and somatic mutations (E and G). (Poduri A, et al. Somatic mutation, genomic variation, and neurological disease. Science. 2013;341(6141). Copyright permission requested) **Image A:** Autosomal dominant inheritance – disease expression with only one mutation from one parents and affects all cells in the gamete. **Image C:** De novo mutation – all cells in gamete contain the mutation but disease expression is in a specific organ. **Image E:** Early post-zygotic mutation – somatic mutation occurring early in gestation with mosaic expression, affecting only a portion of the cells in the fetus. **Image G:** Late post-zygotic mutation – somatic mutation occurring late in gestation with mosaic expression, affecting only certain tissues in the fetus

Sturge-Weber syndrome (facial capillary malformation in trigeminal distribution, leptomeningeal angiomatosis, glaucoma, and seizures), Proteus syndrome (AKT1 gene) [31], CLOVES (**c**ongenital **l**ipomatous **o**vergrowth, **v**ascular malformation, **e**pidermal **n**evus, **s**coliosis), and Klippel-Trenaunay syndrome (PIK3CA) [32]. Entities with PIK3CA somatic mutations are collectively termed "PIK3CA-related overgrowth spectrum (PROS)" which includes diagnosis with or without vascular anomalies [33]. The PIK3-AKT pathway has been shown to be important in the etiology of these syndromes, and medications which inhibit these pathways (e.g., sirolimus) are being studied for patients with vascular anomalies (Fig. 4.3).

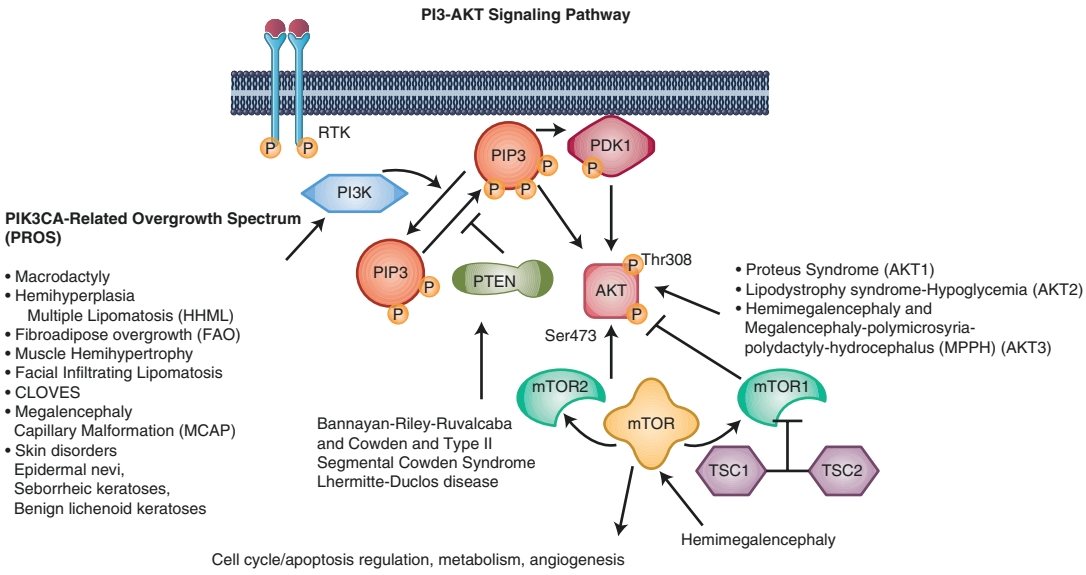

Fig. 4.3 PI3K-AKT pathway and associated clinical overgrowth disorders (Keppler-Noreuil et al. [33]. Creative Commons Attribution License)

Helpful websites to keep apprised of updated information regarding genetic mutations in vascular anomalies include the following resources:

1. OMIM (Online Mendelian Inheritance in Man) is an online catalog of human genes and genetic disorders (http://omim.org).
2. GeneTests (https://www.genetests.org/) is a website which provides genetic information including which tests can be performed for each diagnosis and where the testing is available.
3. GeneCards (http://www.genecards.org/) provides more in-depth scientific data regarding each gene. A mutation database for hereditary hemorrhagic telangiectasia is available at http://arup.utah.edu/database/hht/.
4. Vascular Anomaly and Lymphedema Mutation Database is maintained in Brussels (http://www.icp.ucl.ac.be/vikkula/VAdb/home.php?action=switch_db).

Conclusion

Much progress has been made in identifying causative genes and elaborating molecular pathways pertinent to vascular anomalies. In many cases, testing for relevant genes is not consistently covered by insurance plans. With time, one is hopeful that the clinical relevance of this genetic information will translate into routine (and reimbursable) medical tests.

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