Published in final edited form as:
Lymphat Res Biol. 2005 ; 3(4): 226–233.

Update on the Molecular Genetics of Vascular Anomalies

QING K. WANG, Ph.D., M.B.A.
Department of Molecular Cardiology and Center for Cardiovascular Genetics, The Cleveland Clinic Foundation, Cleveland, Ohio; Huazhong University of Science and Technology Human Genome Research Center, Wuhan, Hubei, People's Republic of China.

Abstract

Genetic factors play a critical role in the pathogenesis of vascular anomalies. Significant advances have been made in recent years in identifying the genetic and molecular determinants of a variety of vascular anomalies using a molecular genetic approach. Several genes for vascular anomalies have been identified. These genes include *AGGF1* for Klippel-Trenaunay syndrome, *RASA1* for capillary malformations, *KRIT1*, *MGC4607*, *PDCD10* for cerebral cavernous malformations, *glomulin* for glomuvenous malformations, *TIE2* for multiple cutaneous and mucosal venous malformations, *VEGFR-3*, *FOXC2*, *NEMO*, *SOX18* for lymphedema or related syndromes, *ENG*, *ACVRLK1*, *MADH4* for HHT or related syndromes, NDP for Coats' disease, *Notch3* for CADASIL, and *PTEN* for Proteus Syndrome. These findings have made genetic testing possible in some clinical cases, and may lead to the development of therapeutic strategies for vascular anomalies. Furthermore, these studies have identified critical genes involved in vascular morphogenesis, and provided fundamental understanding of the molecular mechanisms underlying vasculogenesis and angiogenesis.

The vascular system includes blood vessels and lymphatic vessels. Blood vessels are the first organ formed during embryogenesis, and play critical roles in carrying nutrients, gases, wastes, hormones, metabolites, as well as immune cells, to and from distant actively metabolizing tissues. The formation of blood vessels during embryogenesis starts with vasculogenesis followed by angiogenesis.[1,2] Vasculogenesis refers to the differentiation of endothelial cells by mesoderm cells and subsequent formation of the primary capillary plexus by endothelial cells. The primary capillary plexus later undergoes angiogenesis (sprouting, intussusceptive growth, branching, or regression pruning) to form a complex vascular network. Further development accompanied by recruitment of pericytes and smooth muscle cells and changes in size and mural structure leads to the formation of arteries, capillaries, and veins, each with their own function and characteristics. Lymphatic vessels carry lymph and participate in the nutritional processes of organs, and they originate from blood vessels during embryonic development. Disruption of vessel formation and development results in formation of a heterogeneous group of vascular anomalies.

Vascular anomalies are classified into vascular tumors and vascular malformations[3]. Vascular tumors include hemangiomas of infancy, tufted angiomas, Kaposiform hemangioendotheliomas, infantile hemangioendotheliomas, and spindle cell hemangioendotheliomas. Hemangiomas are the most common tumor of infancy. They are not present at birth, become visible within 1 to 4 weeks of neonatal life, then proliferate, and later regress (involute). Vascular malformations include capillary, venous, arterial, and lymphatic

Address reprint requests to: Qing Wang, Ph.D., Lerner Research Institute/ND40, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, E-mail: wangq2@ccf.org.

This work was supported by NIH grants P50 HL 77107, R01 HL65630 and R01 HL66251, an American Heart Association established Investigator award, and the Chinese Ministry of Science and Technology National High Technology 863 Project No. 2002BA711A07.

malformations, telangiectasia, and combined or mixed vascular malformations. Vascular malformations are usually present at birth, grow proportionally with the patient, and rarely regress.

Little is known about the genetics of hemangiomas except that a locus was reported on chromosome 5q31–35.[4] In addition, one somatic mutation P1147S in *VEGFR2*, a receptor for angiogenic factor VEGF, and another mutation P954S in *VEGFR3* were reported,[5] but the link between these two mutations and the disease remains to be established. In contrast, molecular genetic studies have identified disease-causing genes for a variety of vascular malformations (Table 1). The vascular anomaly genes identified before 2003 have been reviewed previously in this journal by Chaft et al.[6] Here, the author updates the advances made in this field.

GENETICS OF CEREBRAL CAVERNOUS MALFORMATIONS (CCM)

Cerebral cavernous malformations (CCM, MIM #116860) are vascular malformations of the central nervous system. Some cases of CCM are asymptomatic, but others can cause seizures, hemorrhagic stroke, or focal neurological deficit. CCM can occur in a sporadic form as well as a familial form.[7] Familial CCM are inherited in the autosomal dominant mode, and three genes have been localized to chromosome 7q11.2-21 (CCM1, MIM *604214), 7p15-13 (CCM2, #MIM 603284), and 3q25.2-27 (CCM3, MIM #603285).

The disease-causing gene for CCM1 has been identified as *KRIT1* (Krev interaction trapped 1),[8,9] which encodes a protein with a four ankyrin repeat domain at the N-terminus and a C-terminal domain for interaction with Krev-1 (Rap1a, ras-related protein 1A). Many *KRIT1* mutations have been identified in patients with CCM and most of them are loss-of-function mutations. Approximately 40% of CCM families carry *KRIT1* mutations. The N-terminus of KRIT1 also contains an NPXY motif that has been recently shown to interact with ICAP1α, the integrin cytoplasmic domain-associated protein-1α.[10] This interaction competes directly with an interaction between a NPXY motif in the cytoplasmic domain of β1 integrin and ICAP1α[10]. Loss-of function mutations in KRIT1 are expected to lead to increased interaction between ICAP1α and β1 integrin, which influences integrin β1-dependent cell adhesion, migration, and angiogenesis.

The second CCM gene, CCM2, has been identified as a novel gene called *MGC4607* by two independent groups.[11,12] The function of MGC4607 is unknown except that it contains a phosphotyrosine-binding or PTB domain.[11,12] MGC4607 mutations may account for 20% of familial CCM cases.

The CCM3 gene has been identified as *PDCD10* (programmed cell death 10, TFAR15).[13] Approximately 40% of CCM families are linked to the CCM3 locus. *PDCD10* was initially identified as a gene whose expression was up-regulated in the TF-1 premyeloid cell line after growth factor deprivation and in a fibroblast cell line upon apoptosis induction.[14] Its role in vascular morphogenesis remains to be investigated.

GENETICS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA (HHT)

Hereditary hemorrhagic telangiectasia (HHT, MIM #187300) is an autosomal dominant vascular dysplasia characterized by mucocutaneous telangiectases and arteriovenous malformations of skin, mucosa, and viscera (lung, liver, and brain). The frequent complications are epistaxis and gastrointestinal haemorrhage. Previous genetic linkage analysis has identified two loci, HHT1 on chromosome 9q34.1 (MIM #187300) and HHT2 on chromosome 12q11-14 (MIM #600376). HHT1 is caused by mutations in *endoglin* which encodes a TGFβ binding protein expressed predominantly in endothelial cells.[15] Endoglin binds to TGFβ1, TGFβ2, activin-A, BMP2, and BMP7, but not to TGFβ2.[16,17] Endoglin is involved in the TGFβ

signaling pathway, which lays an important role in vascular remodeling and the maintenance of vessel wall integrity.[18] HHT2 results from mutations in the *ALK1* or *ACVRL1* gene which encodes a type 1 serine-threonine kinase receptor in endothelial cells.[19] ALK1 binds to TGFβ1 and activin-A, and signal through phosphorylation of SMAD1 and SMAD5.[20,21] HHT patients with mutations in *endoglin* are associated with a more severe clinical outcome, an earlier onset of epistaxis and telangiectasis, than those with *ALK1* mutations.[22] Pulmonary arteriovenous malformations were detected only in patients with *endoglin* mutations in a cohort study of 49 HHT1 patients and 34 HHT2 patients.[22]

Recently, the third genetic locus for HHT, HHT3, was identified. Cole et al.[23] studied a family in which linkage to *endoglin*, *ALK1*, and *SMAD4* was excluded. A genome-wide scan of the family identified linkage to markers on chromosome 5q31.5-32.[23] The specific HHT gene at this locus has not been identified yet.

HHT associated with juvenile polyposis (JP) has been found to be a distinct syndrome, JP/HHT (MIM #175050). Familial JP can be caused by mutations in the *MADH4* gene on chromosome 18q21.1 which encodes SMAD4.[24] Interestingly, Gallione et al.[24] identified *MADH4* mutations in six unrelated families segregating both JP and HHT. SMAD4 is an integral downstream effector of the TGFβ signal transduction pathway.

Another telangiectasia related disease, Coats' disease or retinal telangiectasis (MIM, #300216) is characterized by a defect of retinal vascular development that results in vessel leakage, sub-retinal exudation, and retinal detachment. Retinal telangiectasis was found to be associated with a somatic mutation in the Norrie disease gene *NDP* on chromosome Xp11.4.[25] *NDP* encodes a protein called norrin, a secreted protein that can bind to receptor Frizzled-4 (Fz4), which may activate a signaling pathway involved in vascular development in the eye and ear.

GENETICS OF KLIPPEL-TRENAUNAY SYNDROME

Klippel-Trenaunay syndrome (KTS, MIM #149000) is a congenital vascular disorder comprised of capillary malformations (98% of KTS patients), venous malformations or varicose veins (72% of patients), and hypertrophy of the affected tissues (67% of the patients), but the presence of two of the three cardinal features is sufficient to make a diagnosis.[26] Most KTS cases are sporadic. Interestingly, three chromosomal abnormalities have been reported in three different KTS patients: two balanced translocations t(5;11)(q13.3;p15.1) and t(8;14)(q22.3;q13), and an extra supernumerary ring chromosome 18[1,27–29]. Translocation t(8;14)(q22.3;q13) and the ring chromosome 18 were shown to arise *de novo*, which strongly suggests that genetic factors contribute to the pathogenesis of KTS. Characterization of cytogenetic abnormalities such as translocations associated with diseases is a very useful approach to identify human disease genes. For translocation t(8;14)(q22.3;q13), the breakpoint on chromosome 8q22.3 has been defined to a <5-cM interval, and the 14q13 breakpoint within a 1-cM region.[29] The specific vascular gene disrupted by either 8q22.3 or 14q13 breakpoints remains to be identified. The ring chromosome 18 r(18) was mostly derived from the short arm of chromosome 18, and further analyses of the genes on the r(18) may lead to the identification of a vascular gene.[28]

Chromosomal breakpoints involved in translocation t(5;11)(q13.3;p15.1) have been fully characterized, which has led to the identification of a susceptibility gene, *AGGF1* (previously known as *VG5Q*), for KTS.[27] *AGGF1* is located on chromosome 5q13.3 and encodes an angiogenic factor.[27] AGGF1 protein contains a coiled-coil motif (amino acids 19–85), an OCRE (OCtamer REpeat) motif (amino acids 197–256), a forkhead-associated domain (FHA, amino acids 435 to 508) and a G-patch domain (amino acids 619–663), but the exact function of each domain remains to be defined. The chromosome 5q13.3 breakpoint is located in the promoter region of AGGF1, and increases the expression of *AGGF1* by three-fold.[27] A

mutation, E133K, in *AGGF1* was identified and was later shown to increase the angiogenic activity of AGGF1. Mutation E133K was established to be associated with KTS using a case-control association study (the frequency of allele K, 3.8% in cases vs. 0% in controls, P = 0.009). These results establish *AGGF1* as the first susceptibility gene that confers a risk to the development of KTS, and suggest that that the molecular mechanism for the pathogenesis of KTS is the "increased" angiogenesis. These results are consistent with histological studies that showed an increase in both the number and diameter of the venules in the dermis and subdermal fat of KTS tissues.[30]

Sporadic occurrence of KTS and a mosaic pattern of KTS features may be explained by the two-hit hypothesis and the concept of paradominant inheritance proposed by Happle.[31–33] Germline mutations in a KTS gene (e.g., *AGGF1*) are important for development of KTS, but not sufficient. A "second hit", somatic mutation in the same KTS gene or in a different gene is required for the development of KTS features.

GENETICS OF LYMPHEDEMA

Hereditary lymphedema (MIM #153100) is characterized by chronic swelling of the extremities by insufficient lymphatic drainage, and is caused by defects in lymphatic vessels, either hypoplasic or hyperplasic. The most common mode of inheritance for hereditary lymphedema is autosomal dominant. The first genetic locus for hereditary lymphedema was mapped to chromosome 5q35, and the disease-causing gene was subsequently identified as the *FLT4* gene which encodes the vascular endothelial growth factor receptor-3, VEGFR3.[34,35] Hereditary lymphedema associated with VEGFR3 mutations or type I hereditary lymphedema is an early-onset lymphedema that is usually present at birth or soon after birth.

The type II hereditary lymphedema (MIM #153200 and #602402) is a late-onset disease with reduced penetrance, variable phenotype, and association with other features including distichiasis, ptosis, cleft palate, yellow nails, and congenital heart disease. It is caused by mutations in the forkhead family transcription factor gene MFH1 (FOXC2) on chromosome 16q24.3.[36–38]

The hypotrichosis-lymphedema-telangiectasia syndrome (HLTS, MIM #607823) is an interesting syndrome of combination of lymphedema with hypotrichosis (sparse hair) and telangiectasia (abnormal dilation of capillaries and arterioles). HLTS is caused by inactivating mutations in the *SOX18* gene which is on chromosome 20q13 and encodes a transcription factor in the *SOX* (Sry-type high-mobility group box) family of transcription factors.[39] Three HLTS families with *SOX18* mutations were reported; two families with a recessive mode of inheritance have homozygous missense mutations, and the one with autosomal dominant HLTS has a nonsense mutation (C240X) that generates a truncated SOX18 protein lacking the transactivation domain.

A rare X-linked recessive syndrome of anhidrotic ectodermal dysplasia with immunodeficiency, osteopetrosis, and lymphedema (OL-EDA-ID, MIM #300301) is caused by stop codon mutations in the *NEMO* gene on chromosome Xq28.[40] *NEMO* encodes the regulatory subunit of the IKK (IkappaB kinase) complex, which is essential for NF-kappaB signaling.

An autosomal recessive syndrome of hereditary recurrent cholestasis and lymphedema (MIM %214900) was reported and a genetic locus was identified on chromosome 15q.[41] The specific gene remains to be identified.

GENETICS OF CAPILLARY MALFORMATIONS

Capillary malformations (CM) or port-wine stains (MIM #163000) are the most common cutaneous vascular malformation that appears as a red macular stain. A genetic locus for CM, CMC1, was mapped to chromosome 5q14-21 in a study of 13 families.[42] Subsequent studies identified the CMC1 gene as the *RASA1* gene which encodes p120-RasGTPase-activating protein (p120-RasGAP). *RASA1* mutations were detected in families with capillary malformations associated with either arteriovenous malformation, arteriovenous fistula, or Parkes Weber syndrome (capillary malformation-arteriovenous malformation, CMAVM)" (MIM #608354).[43] The function of p120-Ras-GAP is to switch the active GTP-bound Ras to the inactive GDP-bound form. Similar to KRIT that causes CCM1 when mutated, p120-Ras-GAP was shown to bind to Krev-1/Rap1a,[44] which is involved in integrin β1-mediated cell adhesion and angiogenesis.

GENETICS OF VENOUS MALFORMATIONS

Venous malformation is a common type of vascular anomaly. Two genes have been identified for venous malformations, *TIE2* for mucocutaneous venous malformations (MIM #600195) and *glomulin* for glomuvenous malformations (MIM #138000). A linkage study of a three generation family with multiple cutaneous and mucosal venous malformations mapped the genetic locus to chromosome 9p21.[45]. The disease-causing gene was later identified as *TIE2* that codes for the endothelial cell-specific receptor tyrosine kinase TIE2, which is a receptor for angiogenic factors angiopoietin-1 (Ang-1) and angiopoietin-2.

Glomuvenous malformations or glomangiomas are venous malformations with smooth muscle-like glomus cells (GVM, MIM #138000). Boon et al.[46] identified the first locus for GVM on chromosome 1p22-p21. The specific gene was later identified as the *glomulin (FAP48)* gene coding for an FK506-binding protein (FKBP)-associated protein of 48 kD.[47] The function of glomulin is unknown.

GENETICS OF CADASIL

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL, MIM #125310) is an inherited cerebrovascular disease characterized by recurrent transient ischemic attacks, strokes, vascular dementia, cognitive deficits, migraine, and psychiatric disorders. Patients with CADASIL show accumulation of electron dense granules (GOM) in the media of arterioles, and extensive cerebral white matter lesions and subcortical infarcts can be detected by MRI. CADASIL is caused by mutations in the *Notch3* gene in the chromosome 19p13 region.[48] The mechanism by which *Notch3* mutations cause CADASIL is not clear. Expression of *Notch3* is highly restricted to vascular smooth muscle cells (VSMC), and is required to generate functional arteries by regulating arterial differentiation and maturation of VSMC.[49]

GENETICS OF PROTEUS SYNDROME

Proteus syndrome (PS, MIM #176920) is a complex hamartomatous disorder which is characterized by connective tissue nevi, epidermal nevi, dysregulated adipose tissue, local overgrowth (macrocephaly, gigantism of hands and feet), subcutaneous tumors, and various vascular anomalies.[50] Common vascular anomalies in PS include vascular tumors, capillary malformations, and venous anomalies (varicosities, prominent veins).[50] About 20% of PS cases and 50% of patients with proteus-like syndrome (PSL) were found to carry germline mutations in the tumor suppressor gene *PTEN* on chromosome 10q23.3.[51] The *PTEN* gene codes for a lipid phosphatase that mediates cell cycle arrest and apoptosis, and is also a gene

responsible for other diseases including 80% of classic Cowden syndrome (CS), and 60% of Bannayan-Riley-Ruvalcaba syndrome (BRRS).[51]

SUMMARY

Molecular genetics has been demonstrated to be a powerful approach for dissecting the etiology of a variety of vascular anomalies. It has provided important insights into the pathogenic mechanisms of many vascular anomalies as well as the molecular mechanisms underlying vascular morphogenesis, growth, and development. A susceptibility gene has been identified for KTS, and disease-causing genes have been identified for cerebral cavernous malformations, HHT, Coats' disease, lymphedema, capillary malformations, multiple cutaneous and mucosal venous malformations, glomuvenous malformations, CADASIL, and Proteus syndrome (see Table 1). Genetic testing is now possible for many patients and/or families with vascular anomalies, which allows more accurate diagnosis and classification of vascular malformations. However, many new genes for vascular anomalies remain to be identified. The future research in the field will focus on (i) identification of new genes for vascular anomalies, (ii) functional characterization of vascular anomaly genes to probe the molecular mechanisms involved in vascular morphogenesis/growth/development, and the pathogenesis of each disease, and (iii) genotype-phenotype correlation studies and other translational studies that will help patients directly. These studies promise to revolutionize vascular medicine, improving the diagnosis and treatment of vascular anomalies.

References

1. Timur AA, Driscoll DJ, Wang Q. Biomedicine and diseases: the Klippel-Trenaunay syndrome, vascular anomalies and vascular morphogenesis. Cell Mol Life Sci 2005;62:1434–1447. [PubMed: 15905966]
2. Risau W. Mechanisms of angiogenesis. Nature 1997;386:671–674. [PubMed: 9109485]
3. Enjolras O, Mulliken JB. Vascular tumors and vascular malformations (new issues). Adv Dermatol 1997;13:375–423. [PubMed: 9551150]
4. Walter JW, Blei F, Anderson JL, Orlow SJ, Speer MC, Marchuk DA. Genetic mapping of a novel familial form of infantile hemangioma. Am J Med Genet 1999;82:77–83. [PubMed: 9916848]
5. Walter JW, North PE, Waner M, Mizeracki A, Blei F, Walker JW, Reinisch JF, Marchuk DA. Somatic mutation of vascular endothelial growth factor receptors in juvenile hemangioma. Genes Chromosomes Cancer 2002;33:295–303. [PubMed: 11807987]
6. Chaft JE, Steckman DA, Blei F. Genetics of vascular anomalies: an update. Lymphat Res Biol 2003;1:283–289. [PubMed: 15624556]
7. Rigamonti D, Hadley MN, Drayer BP, Johnson PC, Hoenig-Rigamonti K, Knight JT, Spetzler RF. Cerebral cavernous malformations. Incidence and familial occurrence . N Engl J Med 1988;319:343–347. [PubMed: 3393196]
8. Labergele Couteulx S, Jung HH, Labauge P, Houtteville JP, Lescoat C, Cecillon M, Marechal E, Joutel A, Bach JF, Tournier-Lasserve E. Truncating mutations in CCM1, encoding KRIT1, cause hereditary cavernous angiomas. Natl Genet 1999;23:189–193.
9. Sahoo T, Johnson EW, Thomas JW, Kuehl PM, Jones TL, Dokken CG, Touchman JW, Gallione CJ, Lee-Lin SQ, Kosofsky B, Kurth JH, Louis DN, Mettler G, Morrison L, Gil-Nagel A, Rich SS, Zabramski JM, Boguski MS, Green ED, Marchuk DA. Mutations in the gene encoding KRIT1, a Krev-1/rap1a binding protein, cause cerebral cavernous malformations (CCM1). Hum Mol Genet 1999;8:2325–2333. [PubMed: 10545614]
10. Zhang J, Clatterbuck RE, Rigamonti D, Chang DD, Dietz HC. Interaction between krit1 and icap1alpha infers perturbation of integrin beta1-mediated angiogenesis in the pathogenesis of cerebral cavernous malformation. Hum Mol Genet 2001;10:2953–2960. [PubMed: 11741838]
11. Denier C, Goutagny S, Labauge P, Krivosic V, Arnoult M, Cousin A, Benabid AL, Comoy J, Frerebeau P, Gilbert B, Houtteville JP, Jan M, Lapierre F, Loiseau H, Menei P, Mercier P, Moreau JJ, Nivelon-Chevallier A, Parker F, Redondo AM, Scarabin JM, Tremoulet M, Zerah M, Maciazek

J, Tournier-Lasserve E. Mutations within the MGC4607 gene cause cerebral cavernous malformations. Am J Hum Genet 2004;74:326–337. [PubMed: 14740320]

12. Liquori CL, Berg MJ, Siegel AM, Huang E, Zawistowski JS, Stoffer T, Verlaan D, Balogun F, Hughes L, Leedom TP, Plummer NW, Cannella M, Maglione V, Squitieri F, Johnson EW, Rouleau GA, Ptacek L, Marchuk DA. Mutations in a gene encoding a novel protein containing a phosphotyrosine-binding domain cause type 2 cerebral cavernous malformations. Am J Hum Genet 2003;73:1459–1464. [PubMed: 14624391]
13. Bergametti F, Denier C, Labauge P, Arnoult M, Boetto S, Clanet M, Coubes P, Echenne B, Ibrahim R, Irthum B, Jacquet G, Lonjon M, Moreau JJ, Neau JP, Parker F, Tremoulet M, Tournier-Lasserve E. Mutations within the programmed cell death 10 gene cause cerebral cavernous malformations. Am J Hum Genet 2004;76:42–51. [PubMed: 15543491]
14. Busch CR, Heath DD, Hubberstey A. Sensitive genetic biomarkers for determining apoptosis in the brown bullhead (*Ameiurus nebulosus*). Gene 2004;329:1–10. [PubMed: 15033523]
15. McAllister KA, Grogg KM, Johnson DW, Gallione CJ, Baldwin MA, Jackson CE, Helmbold EA, Markel DS, McKinnon WC, Murrell J. Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Natl Genet 1994;8:345–351.
16. Barbara NP, Wrana JL, Letarte M. Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-beta superfamily. J Biol Chem 1999;274:584–594. [PubMed: 9872992]
17. Cheifetz S, Bellon T, Cales C, Vera S, Bernabeu C, Massague J, Letarte M. Endoglin is a component of the transforming growth factor-beta receptor system in human endothelial cells. J Biol Chem 1992;267:19027–19030. [PubMed: 1326540]
18. Lebrin F, Deckers M, Bertolino P, Ten DP. TGF-beta receptor function in the endothelium. Cardiovasc Res 2005;65:599–608. [PubMed: 15664386]
19. Johnson DW, Berg JN, Baldwin MA, Gallione CJ, Marondel I, Yoon SJ, Stenzel TT, Speer M, Pericak-Vance MA, Diamond A, Guttmacher AE, Jackson CE, Attisano L, Kucherlapati R, Porteous ME, Marchuk DA. Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Natl Genet 1996;13:189–195.
20. Chen YG, Massague J. Smad1 recognition and activation by the ALK1 group of transforming growth factor-beta family receptors. J Biol Chem 1999;274:3672–3677. [PubMed: 9920917]
21. Macias-Silva M, Hoodless PA, Tang SJ, Buchwald M, Wrana JL. Specific activation of Smad1 signaling pathways by the BMP7 type I receptor, ALK2. J Biol Chem 1998;273:25628–25636. [PubMed: 9748228]
22. Berg J, Porteous M, Reinhardt D, Gallione C, Holloway S, Umasunthar T, Lux A, McKinnon W, Marchuk D, Guttmacher A. Hereditary haemorrhagic telangiectasia: a questionnaire based study to delineate the different phenotypes caused by endoglin and ALK1 mutations. J Med Genet 2003;40:585–590. [PubMed: 12920067]
23. Cole SG, Begbie ME, Wallace GM, Shovlin CL. A new locus for hereditary haemorrhagic telangiectasia (HHT3) maps to chromosome 5. J Med Genet 2005;42:577–582. [PubMed: 15994879]
24. Gallione CJ, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, Mitchell G, Drouin E, Westermann CJ, Marchuk DA. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). Lancet 2004;363:852–859. [PubMed: 15031030]
25. Black GC, Perveen R, Bonshek R, Cahill M, Clayton-Smith J, Lloyd IC, McLeod D. Coats' disease of the retina (unilateral retinal telangiectasis) caused by somatic mutation in the NDP gene: a role for norrin in retinal angiogenesis. Hum Mol Genet 1999;8:2031–2035. [PubMed: 10484772]
26. Jacob AG, Driscoll DJ, Shaughnessy WJ, Stanson AW, Clay RP, Gloviczki P. Klippel-Trenaunay syndrome: spectrum and management. Mayo Clin Proc 1998;73:28–36. [PubMed: 9443675]
27. Tian XL, Kadaba R, You SA, Liu M, Timur AA, Yang L, Chen Q, Szafranski P, Rao S, Wu L, Housman DE, DiCorleto PE, Driscoll DJ, Borrow J, Wang Q. Identification of an angiogenic factor that when mutated causes susceptibility to Klippel-Trenaunay syndrome. Nature 2004;427:640–645. [PubMed: 14961121]

28. Timur AA, Sadgephour A, Graf M, Schwartz S, Libby ED, Driscoll DJ, Wang Q. Identification and molecular characterization of a de novo supernumerary ring chromosome 18 in a patient with Klippel-Trenaunay syndrome. Annu Hum Genet 2004;68:353–361.
29. Wang Q, Timur AA, Szafranski P, Sadgephour A, Jurecic V, Cowell J, Baldini A, Driscoll DJ. Identification and molecular characterization of de novo translocation t(8;14)(q22.3;q13) associated with a vascular and tissue overgrowth syndrome. Cytogenet Cell Genet 2001;95:183–188. [PubMed: 12063397]
30. Baskerville PA, Ackroyd JS, Browse NL. The etiology of the Klippel-Trenaunay syndrome. Annu Surg 1985;202:624–627.
31. Happle R. Cutaneous manifestation of lethal genes. Hum Genet 1986;72:280. [PubMed: 3957353]
32. Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. J Am Acad Dermatol 1987;16:899–906. [PubMed: 3033033]
33. Happle R. Klippel-Trenaunay syndrome: is it a paradominant trait? Br J Dermatol 1993;128:465–466. [PubMed: 8388238]
34. Irrthum A, Karkkainen MJ, Devriendt K, Alitalo K, Vikkula M. Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyro-sine kinase. Am J Hum Genet 2000;67:295–301. [PubMed: 10856194]
35. Karkkainen MJ, Ferrell RE, Lawrence EC, Kimak MA, Levinson KL, McTigue MA, Alitalo K, Finegold DN. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. Natl Genet 2000;25:153–159.
36. Bell R, Brice G, Child AH, Murday VA, Mansour S, Sandy CJ, Collin JR, Brady AF, Callen DF, Burnand K, Mortimer P, Jeffery S. Analysis of lymphoedema-distichiasis families for FOXC2 mutations reveals small insertions and deletions throughout the gene. Hum Genet 2001;108:546–551. [PubMed: 11499682]
37. Fang J, Dagenais SL, Erickson RP, Arlt MF, Glynn MW, Gorski JL, Seaver LH, Glover TW. Mutations in FOXC2 (MFH-1), a forkhead family transcription factor, are responsible for the hereditary lymphedema-distichiasis syndrome [In Process Citation]. Am J Hum Genet 2000;67:1382–1388. [PubMed: 11078474]
38. Finegold DN, Kimak MA, Lawrence EC, Levinson KL, Cherniske EM, Pober BR, Dunlap JW, Ferrell RE. Truncating mutations in FOXC2 cause multiple lymphedema syndromes. Hum Mol Genet 2001;10:1185–1189. [PubMed: 11371511]
39. Irrthum A, Devriendt K, Chitayat D, Matthijs G, Glade C, Steijlen PM, Fryns JP, Van Steensel MA, Vikkula M. Mutations in the transcription factor gene SOX18 underlie recessive and dominant forms of hypotrichosis-lymphedema-telangiectasia. Am J Hum Genet 2003;72:1470–1478. [PubMed: 12740761]
40. Doffinger R, Smahi A, Bessia C, Geissmann F, Feinberg J, Durandy A, Bodemer C, Kenwrick S, Dupuis-Girod S, Blanche S, Wood P, Rabia SH, Headon DJ, Overbeek PA, Le DF, Holland SM, Belani K, Kumararatne DS, Fischer A, Shapiro R, Conley ME, Reimund E, Kalhoff H, Abinun M, Munnich A, Israel A, Courtois G, Casanova JL. X-linked anhidrotic ectodermal dysplasia with immunodeficiency is caused by impaired NF-kappaB signaling. Natl Genet 2001;27:277–285.
41. Bull LN, Roche E, Song EJ, Pedersen J, Knisely AS, van Der Hagen CB, Eiklid K, Aagenaes O, Freimer NB. Mapping of the locus for cholestasis-lymphedema syndrome (Aagenaes syndrome) to a 6.6-cM interval on chromosome 15q. Am J Hum Genet 2000;67:994–999. [PubMed: 10968776]
42. Eerola I, Boon LM, Watanabe S, Grynberg H, Mulliken JB, Vikkula M. Locus for susceptibility for familial capillary malformation (‘port-wine stain’) maps to 5q. Eur J Hum Genet 2002;10:375–380. [PubMed: 12080389]
43. Eerola I, Boon LM, Mulliken JB, Burrows PE, Domp-martin A, Watanabe S, Vanwijck R, Vikkula M. Capillary malformation-arteriovenous malformation, a new clinical and genetic disorder caused by RASA1 mutations. Am J Hum Genet 2003;73:1240–1249. [PubMed: 14639529]
44. Frech M, John J, Pizon V, Chardin P, Tavitian A, Clark R, McCormick F, Wittinghofer A. Inhibition of GTPase activating protein stimulation of Ras-p21 GTPase by the Krev-1 gene product. Science 1990;249:169–171. [PubMed: 2164710]

45. Boon LM, Mulliken JB, Vikkula M, Watkins H, Seidman J, Olsen BR, Warman ML. Assignment of a locus for dominantly inherited venous malformations to chromosome 9p. Hum Mol Genet 1994;3:1583–1587. [PubMed: 7833915]

46. Boon LM, Brouillard P, Irrthum A, Karttunen L, Warman ML, Rudolph R, Mulliken JB, Olsen BR, Vikkula M. A gene for inherited cutaneous venous anomalies ("glomangiomas") localizes to chromosome 1p21-22. Am J Hum Genet 1999;65:125–133. [PubMed: 10364524]

47. Brouillard P, Boon LM, Mulliken JB, Enjolras O, Ghassibe M, Warman ML, Tan OT, Olsen BR, Vikkula M. Mutations in a novel factor, glomulin, are responsible for glomuvenous malformations ("glomangiomas"). Am J Hum Genet 2002;70:866–874. [PubMed: 11845407]

48. Joutel A, Corpechot C, Ducros A, Vahedi K, Chabriat H, Mouton P, Alamowitch S, Domenga V, Cecillion M, Marechal E, Maciazek J, Vayssiere C, Cruaud C, Cabanis EA, Ruchoux MM, Weissenbach J, Bach JF, Bousser MG, Tournier-Lasserve E. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. Nature 1996;383:707–710. [PubMed: 8878478]

49. Domenga V, Fardoux P, Lacombe P, Monet M, Maciazek J, Krebs LT, Klonjkowski B, Berrou E, Mericskay M, Li Z, Tournier-Lasserve E, Gridley T, Joutel A. Notch3 is required for arterial identity and maturation of vascular smooth muscle cells. Genes Dev 2004;18:2730–2735. [PubMed: 15545631]

50. Hoeger PH, Martinez A, Maerker J, Harper JI. Vascular anomalies in Proteus syndrome. Clin Exp Dermatol 2004;29:222–230. [PubMed: 15115498]

51. Eng C. PTEN: one gene, many syndromes. Hum Mutat 2003;22:183–198. [PubMed: 12938083]

Table 1

Genetics of Vascular Anomalies

Vascular anomaly	*Chromosomal location*	*Gene*	*OMIM #*
Type 1 Cerebral cavernous malformation (CCM1)	7q11.2-q21	*KRIT1*	#116860 and *604214
Type 2 Cerebral cavernous malformation (CCM2)	7p15-p13	*MGC4607*	#603284
Type 3 Cerebral cavernous malformation (CCM3)	3q25.2-27	*PDCD10*	#603285
Type 1 Hereditary hemorrhagic telangiectasia (HHT1)	9q34.1	*Endoglin (ENG)*	#187300 and *131195
Type 2 Hereditary hemorrhagic telangiectasia (HHT2)	12q11-q14	*ALK1*(*ACVRLK1*)	#600376 and *601284
Type 3 Hereditary hemorrhagic telangiectasia (HHT3)	5q31.5-32	?	?
Juvenile polyposis/hereditary hemorrhagic telangiectasia	18q21.1	*MADH4* (*SMAD4*)	#170550 and *600993
Coats' disease (Retinal telangiectasis)	Xp11.4	*NDP*	#300216 and +310600
Klippel-Trenaunay syndrome (KTS)	5q13.3	*AGGF1*	#149000 and *608464
Lymphedema type I (Nonne-Milroy lymphedema)	5q35.3	*VEGFR3*	#153100 and *136352
Lymphedema type I (Lymphedema-distichiasis syndrome)	16q24.3	*FOXC2*	#153200 and +602402
Hypotrichosis-lymphedema-telangiectasia syndrome (HLTS)	20q13.33	*SOX18*	#607823
OL-EDA-ID syndrome (osteopetrosis and lymphedema, ectodermal dysplasia, anhidrotic, with immunodeficiency)	Xq28	*NEMO*	#300301
Cholestasis-lymphedema syndrome	15q	?	%214900
Capillary malformation-arteriovenous malformation (CMAVM)	5q13.3	*RASA 1*	%163000 and #608354
Venous malformations, multiple cutaneous and mucosal (VMCM)	9p21	*TIE2*	#600195
Glomuvenous malformations (GVM)	1p22-p21	*Glomulin*	#138000
Cerebral arteriopathy (CADASIL)	19p13.2-p13.1	*Notch3*	#125310 and *600276
Proteus syndrome	10q23.31	*PTEN*	#176920 and *601728

OMIM, Online Mendelian Inheritance in Man: http://www.ncbi.nlm.nih.gov/omim/