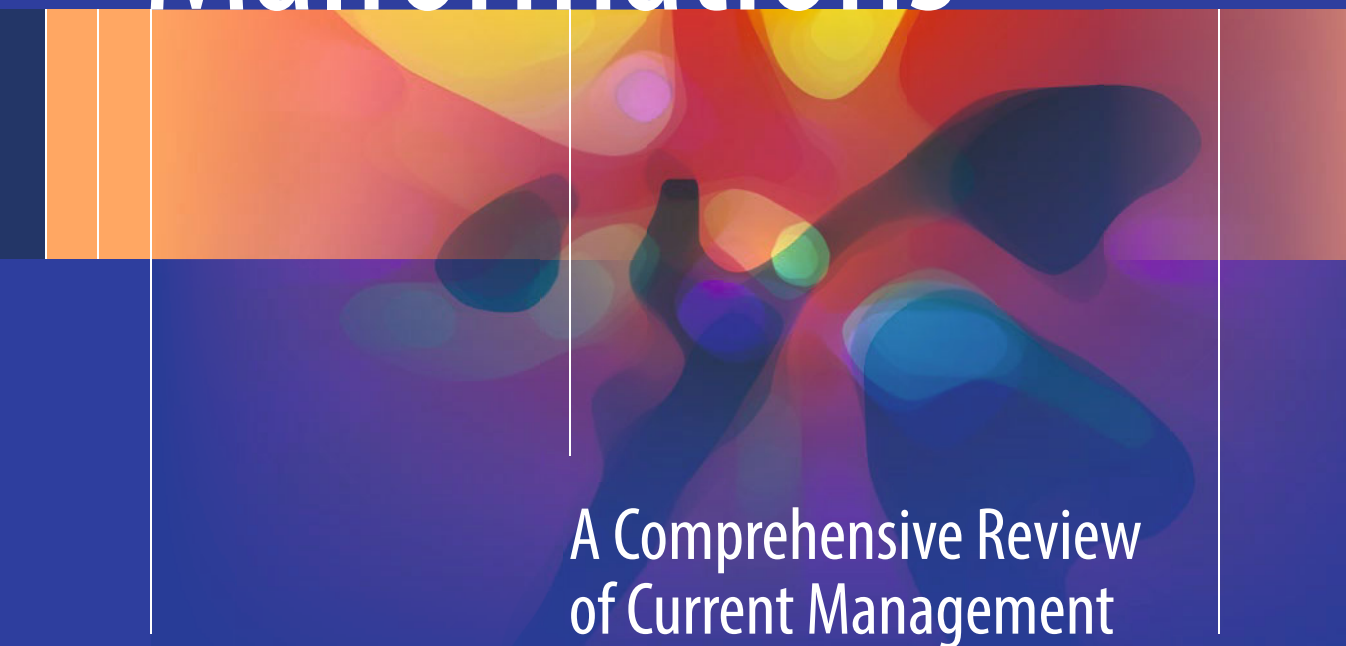
Young-Wook Kim · Byung-Boong Lee
Wayne F. Yakes · Young-Soo Do *Editors*

Congenital Vascular Malformations



A Comprehensive Review of Current Management

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Foreword

It is with genuine pleasure that I write this Foreword for a book whose material has been painstakingly studied, treated, and collected during several decades by a multidisciplinary cadre of dedicated physicians deeply interested in a discipline that has not been the favorite among our colleagues in the medical field.

As I have written elsewhere[1], "our three vascular systems, arterial, venous and lymphatic, form a complex seamless network of miles of intricate vessels with specific vital physiologic functions. They intertwine, twist and cross in different directions continuously moving large volumes of blood and lymph. These systems are critically important for our normal life. By the miracle of nature, they are automatically separated from each other at birth. However, due to still obscure genetic derangement, distorted errors of nature result in vascular anomalies. After birth, these systems may maintain their fetal characteristics and produce either diffuse or circumscribed clusters of vessels where arteries and veins are still connected mixing arterial with venous blood (arteriovenous shunts) or mixed venous and lymphatic vessels as occurs in cases of malformations of veno-lymphatic predominance such as in the syndrome of Klippel-Trenaunay."

Since their initial description, congenital vascular malformations have been a difficult and complicated sector of the vascular system. They have always been a classification, diagnostic, and therapeutic challenge, and therein lies the reason for their mysterious and captivating attraction to a group of masochistic physicians who love the challenge of a bizarre, malformed limb or a disfiguring craniofacial malformation. It is not necessary for me to delve deeply into the reasons that have rekindled the interest in the field of vascular anomalies to recognize that the diagnosis and management of this large group of diseases has had a monumental impulse with the radiological, endovascular, and genetic revolutions.

In the year 1996, I received an invitation from Professor B.B. Lee, a coeditor of this book and at that time chairman of the Department of Surgery at Samsung Medical Center in Seoul South Korea, to visit his Department. During the week that I spent with Dr. Lee's team, I made daily rounds seeing patients with an array of vascular malformations and observing some

[1] Villavicencio JL. Classification of peripheral arteriovenous and venous malformations. A review. In: Stanley J, Veith JF, Wakefield TW editors. Therapy in vascular and endovascular surgery 5th ed. Elsevier Saunders, Philadelphia; 2014. p 829–30.

challenging cases being thoroughly investigated and treated using ethanol and other therapeutic modalities. I was witnessing the birth of an outstanding multidisciplinary group of physicians interested in tackling the challenging group of anomalies of the vascular system. Throughout the years, this group has become one of the leading centers in the world for the study, investigation, and management of congenital vascular malformations. I had the opportunity to verify my previous statement during a second visit in 2004. I met then Professor Young-Wook Kim and most of the coauthors of this book. Dr. Lee had surrounded himself by a group of several prestigious investigators such as the late Dr. John Bergan, Corinne Becker, Dirk Loose, Wayne Yakes, and Raul Mattassi, just to mention a few. Through visits to Seoul and conferences with his team, these experts contributed to cement the basis for the creation of a first-class center for the study and care of patients with congenital vascular malformations. This book is the proud child of those efforts. It is rewarding indeed to notice the renovated interest that this subject has had in recent years with its inclusion in excellent international symposiums dedicated to congenital vascular anomalies in the most important congresses of the world.

The authors of this book ought to be commended for their effort. I am sure that this book will find a warm welcome among many of our puzzled colleagues facing a child with a monstrous vascular malformation and will guide and assist them in finding the best possible tactic to assist their patient. Behind its pages, as a solid shield, lays the experience and expertise of the collaborators who are compassionate experts who have experienced the great satisfaction of seeing again the smile of an afflicted patient.

Washington DC, USA J. Leonel Villavicencio, MD, FACS

Preface

It has been a long way since we dared to challenge the enigma of modern medicine, especially in congenital vascular malformations (CVMs). Indeed, it took over 20 years for us to master these ever-confusing vascular birth defects, starting from scratch like a blind man feeling an elephant.

Taking the advantage of unconditional support by the newly founded institute Samsung Medical Center, we were able to organize a dream team including so many world experts of multispecialty we invited from the four corners of the world as critical consultants and became a world leading group within a decade.

Finally, based on extraordinary experiences we accumulated through the last two decades with nearly 3000 patients, we were able to organize *Handbook of Congenital Vascular Malformation* with so many collaborators to share this hard-earned dividend with the rest of our colleagues who were not as fortunate as we were.

Indeed, CVMs are still the most confusing type of vascular disorder showing thousands of different faces due to their nature as vascular embryonal developmental anomalies. These anomalies as the outcome of developmental arrest from various stages of embryogenesis affect all three circulation systems so that they present an extreme variety of clinical manifestations in arteries, veins, lymphatics, and/or cutaneous/capillary vasculature throughout the body in various combinations.

Therefore, the CVM patients would present not only the primary lesion, either as an independent or mixed/combined condition, but also the secondary complications and morbidity caused by the primary lesion.

CVM is often found scattered throughout the body in varying extent and severity with varying symptoms and signs and become clinically detectable in various ages throughout life. Therefore, these CVM patients with extreme age distribution from infant to old age with garden-variety complaints would wind up seeking for help from a vast array of clinicians/specialties such as vascular surgery, orthopedic surgery, and plastic surgery, as well as pediatrics and other specialties. Hence, CVMs remain an enigma, difficult to define including the specialty dealing with this unique disease process.

In the past, before modern contemporary concept was established, even for those who became interested in CVMs, it was virtually impossible to comprehend all of the different forms of malformations. Definition and classification of the CVMs then were based only on singular if not sporadic anecdotal experiences at best so that the nature of these unique developmental

defects was scantly understood and studied/documented purely based on the clinical findings alone.

It must have been as if observing a subject through a small buttonhole without realizing the whole subject. But through the last three decades in particular, the old concept of the CVMs established on name-based eponyms has been successfully replaced with contemporary concept with new definition and classification based on current advanced diagnostic and therapeutic technology.

Through these trials and tribulations, the current understanding of CVM has grown by leaps and bounds for the last two decades and continues to accelerate at a blinding rate. Mandated research in this unique field has grown exponentially to include understanding of the development of fetal vascular systems using animal research protocols as well as understanding of CVM pathogenesis at molecular or submolecular levels through human embryology research.

Nevertheless, therapeutic modalities of CVM have been far from being satisfactory. The surgical/excisional treatment with chance of cure is extremely limited by significantly high recurrence rates due to their nature. The outcome of deep-seated infiltrating lesion in particular is still far from satisfactory despite the variety of endovascular sclerotherapies or embolotherapies.

Some of the leading sclerosing agents, for example, have such restrictions and limitations with many serious side effects including systemic toxicity and extravasation causing further perivascular tissue damage.

In light of current difficulties in clinical practices associated with CVM, we invited world-renowned CVM specialists throughout the international community for each carefully selected topic/issue to share their experiences and elucidate the current state of understanding in CVM classification, pathogenesis, clinical features, diagnostic approaches, treatment of the lesions, and management of their complications.

Indeed, all our collaborator colleagues gave such generous donation of their time and knowledge unconditionally with no proper compensation; we are eternally grateful.

To conclude, we also would like to acknowledge and offer our heart-filled gratitude to those researchers and medical practitioners who have paved the way for continued enrichment of knowledge and understanding of the CVM. Furthermore, even with the shortcomings that we acknowledge associated with the treatment and understanding of this disease process, for those who entrust themselves to us for treatment, we would like to offer sincere gratitude to them as well.

Lastly, it is with our utmost desire that this book becomes a valuable source of understanding of this relatively uncommon vascular disorder, congenital vascular malformations, to those students as well as clinical practitioners who may have an interest in CVM.

Seoul, South Korea — Young-Wook Kim
Bethesda, MD, USA — Byung-Boong Lee
Seoul, South Korea — Young-Su Do
Englewood, CO, USA — Wayne Yakes

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Part I

Introduction

Congenital Vascular Malformations: An Historical Account

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J. Leonel Villavicencio

An Overview

Mild as well as severe vascular anomalies have been described in ancient documents by authors such as Hippocrates [1], Ambrose Pare [2], Galen [3], and others.

Some anomalies have been named after those who first described them, such as the Klippel-Trenaunay, Maffucci, Servelle, Martorell, and Parkes Weber syndromes. Others have been named after Greek or Roman mythological monstrosities. As we review the features and names of some of the congenital vascular anomalies heretofore described, we cannot avoid but to notice the striking relationship with creatures and myths of the Greek and Roman mythology. It is fascinating to review the Pantheon of Greek and Roman gods and realize that the monstrous aspect and names of some of the congenital vascular anomalies that we observe in our clinics were often inspired by mythological creatures.

The cirsoid aneurysm of the scalp, an arteriovenous malformation, resembles Medusa's head where the hair was replaced by a nest of snakes [4], and the caput medusae, a net of paraumbilical veins, is formed in patients with portal hypertension due to liver cirrhosis. The sirenomelia, a severe and often fatal congenital anomaly, received its name by its resemblance to the Sirens mythological creatures [5]. Let's review the reasons behind these names.

> The Sirens were beautiful but dangerous creatures that lured the sailors with their beautiful voices to their doom, causing the ships to crash on the reefs near their island. They were the daughters of the river god Achelous while their mother may have been Terpsichore the music goddess. Although closely linked to marine environments, they were not considered sea deities. The Sirens were probably considered companions of Persephone, daughter of the goddess Demeter. The latter had given them wings in order to protect her daughter; however, after Persephone's abduction from Hades, Demeter cursed them. The Siren's song was a beautiful but sad melody eternally calling for Persephone's return.
>
> The Argonauts encountered the Sirens but successfully evaded them; Orpheus who was on board, started playing his lyre so beautifully that his music completely drowned the Sirens' song. The tenth century Byzantine encyclopedia Suda says that from their chests up, Sirens had the form of sparrows, below, they were women, or alternatively, that they were little birds with women's faces (Fig. 1.1).
>
> The Sirens of Greek mythology, are sometimes portrayed as fully aquatic and mermaid-like. The facts that in Spanish, French, Italian, and Portuguese the word for mermaid is respectively Sirena, Sirene, Syrena, Sereia, and that in Biology the Serenia comprises an order of fully aquatic mammals that include the manatee, adds to the confusion.

Sirenomelia, also known as mermaid syndrome, is a rare congenital malformation in

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Fig. 1.1 Medusa's head severed by Perseus [4]

which the legs are fused giving them the appearance of a mermaid tail (Fig. 1.2). This condition is found in approximately one out of 100,000 live births (about as rare as conjoined twins) and is usually fatal within a day or two after birth due to complications associated with abnormal kidney and urinary bladder development and function. More than half the cases of sirenomelia result in stillbirth, and this condition is more likely to occur in identical twins than in single births or fraternal twins. It is due to a failure of the normal vascular supply from the lower aorta in utero. Maternal diabetes has been associated with "caudal regression syndrome and sirenomelia" although a few sources question this association [5–8].

> Medusa was a monster, one of the Gorgon sisters and daughter of Phorkys and Keto, the children of Gaea (Earth) and Oceanus (Ocean). She had the face of an ugly woman with snakes instead of hair; anyone who locked into her eyes was immediately turned to stone. Her sisters were Sthenno and Euryale, but Medusa was the only mortal of the three.
>
> Medusa was originally a golden-haired, fair maiden, who, as a priestess of Athena, was devoted to a life of celibacy; however, after being wooed by Poseidon and falling for him, she forgot her vows and married him. For this offense, she was punished by the goddess in a most terrible manner. Each wavy lock of the beautiful hair that had charmed her husband, was changed into a venomous snake; her once gentle love-inspiring eyes turned into blood-shot, furious orbs, which incited fear and disgust in the mind of the onlooker; whilst her former roseate hue and milk white skin assumed a loathsome greenish tinge (Fig. 1.3).
>
> Seeing herself transformed into such a repulsive creature, Medusa fled her home never to return. Wandering about, abhorred, dreaded, and shunned by the rest of the world she turned into a character worthy of her outer appearance. In her despair, she fled to Africa where, while wandering restlessly from place to place, young snakes dropped from her hair; that is how according to the ancient Greeks, Africa became a hotbed of venomous reptiles. With the curse of Athena upon her, she turned into stone whomever she gazed upon, till at last, after a life of nameless misery, deliverance came to her in the shape of death at the hands of Perseus.

As I have written on the subject before [9].

We must recognize those who preceded us trying to sort out the large variety and complexity of the congenital vascular malformations. In 1863, the German pathologist Rudolf Virchow in an effort to establish some kind of order into the maze of this pathology, called "angiomas" to all vascular malformations. He divided them into simplex, cavernosum and racemosum. This terminology was recognized in the Anglo-Saxon writings and thinking during the entire century [10].

Edmondo Malan categorized the vascular malformations according to their embryological characteristics and in 1974 published a scholarly written monograph where he classified 451 cases of vascular anomalies that he studied and treated in: predominantly venous, predominantly arterial, predominantly arterio-venous and predominantly lymphatic. Each of these categories could be localized, or diffuse" [11].

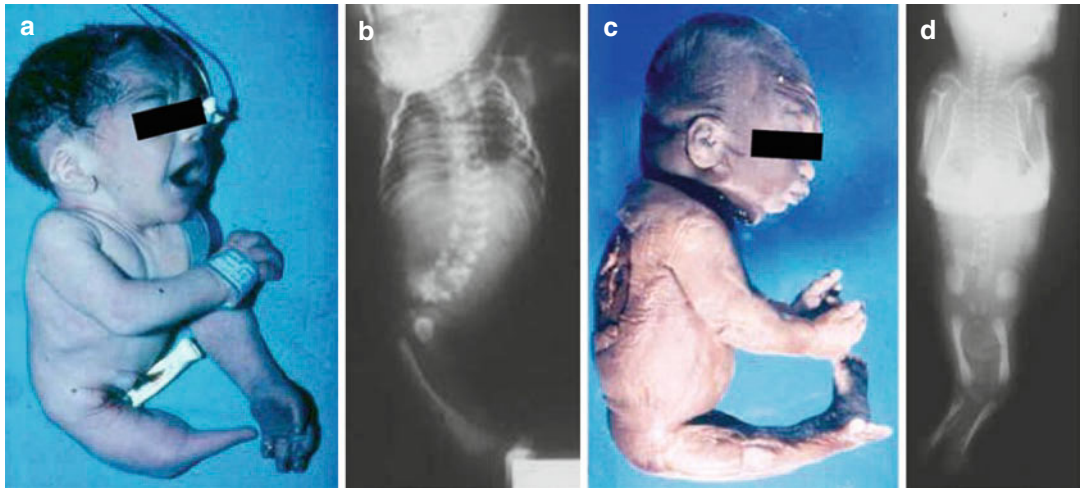

Fig. 1.2 Sirenomelia [6]. Fusion of lower extremities (**a**) Newborn child with sirenomelia (**b**) Total body film showing the fusion of the lower extremities and bone abnormalites (**c**) Lateral view of a fetus with complete fusion of both lower exremities (**d**) Total body Xray of child showing both poorly developed lower extremities fused

Fig. 1.3 The mythological sirens. Winged aquatic women

Efforts of classification, however, have only contributed to increase confusion among physicians who are often bewildered by the bizarre and often grotesque presentation of congenital vascular anomalies. There is in this book a section dedicated to the very important topic of classification of congenital vascular anomalies, and for that reason, we will not dwell into this subject.

> Great progress has occurred during the last 50 years in the puzzling field of the congenital vascular anomalies. My trip into this challenging pathology began in 1957 in Boston. Throughout these years I have been fortunate to observe that in spite of the often repugnant aspect of some patients afflicted by these malformations, there is a group of physicians who have realized that we are here to care for those who cannot care for themselves and who in desperation turn their eyes to us hoping to find relief [9].

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2 Embryological Background of Congenital Vascular Malformations

Hiroo Suami and Byung-Boong Lee

Introduction

The study of the embryological development of the circulatory system began in earnest during the nineteenth century. Early pioneer researchers in this field used intravascular injection of various dye solutions of India ink, silver nitrate, and Prussian blue for demonstration of minute vessels [1, 2]. The injected tissues were fixed and histological investigation was conducted. The researchers' extensive and careful observations enabled them to map the development of the vascular and lymphatic systems in both humans and other mammals.

During the development of the arterial system, construction of aortic arch goes through the most complicated process and is thus recognized as the key to most congenital vascular malformations. The aortic arch originates from symmetrical brachial arches. After tremendous alteration, involving systemic and segmental fusion and separation, the brachial arches transform into the aortic arch. Rathke's diagram is useful and provides a general idea of which components persist and which degenerate to enable transformation into the matured structure [3].

In the development of the venous system, formation of paired anterior and posterior cardinal veins is a significant event. The paired veins take on the important roles of blood drainage in this early developmental stage, but most of their parts degenerate after completion of their roles. Formation of the inferior vena cava is a complex process. Chronological diagrams by McClure and Butler demonstrate precisely how the primitive venous system transforms into the inferior vena cava [4]. Following a sequential, elaborate process, any misplaced degenerations trigger rerouting of blood drainage to the heart and cause persistence of the primary veins.

Sabin used swine embryos and Lewis used rabbit embryos to investigate the development of the lymphatic system [5, 6]. They proposed that the lymphatic system originates from several sites on the primary vein and sprouts centrifugally. In contrast, Huntington and McClure proposed that lymphatic vessels arise in the mesenchymal tissue, independently from the primary veins, growing centripetally, and then subsequently connecting to the venous system [7]. A recent study using molecular markers suggests that in fact both centripetal and centrifugal growths appear to contribute to the development of the lymphatic system [8].

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Maldevelopment of the lymphatic system causes dysfunction of interstitial fluid drainage, namely, heredity or primary lymphedema.

Development of the Blood Vascular System

The blood vascular system develops in two distinct, consecutive phases: (1) vasculogenesis, the de novo differentiation of blood vessels from mesoderm-derived precursor cells, and (2) angiogenesis, the remodeling of these vessels to form arteries and veins [9].

Vasculogenesis first occurs in the yolk sac. Structures called blood islands form as hemangioblasts differentiate into endothelial and red blood cells. The endothelial cells migrate from the blood islands and form a random vascular network called the capillary plexus. Meanwhile, the dorsal aorta forms inside the embryo; eventually, it connects the heart to the capillary plexus of the yolk sac thus completing the circulation loop.

In human embryos, angiogenesis begins at day 21 of embryogenesis, when the heart begins to beat and blood starts circulating in the capillary plexus. Biomechanical and hemodynamic input induces active vascular remodeling. The capillary plexus is remodeled into a functional structure that includes large-caliber vessels for low-resistance rapid flow and small-caliber capillaries for diffusional flow. This remodeling occurs by the regression, sprouting, splitting, or fusion of preexisting vessels. Endothelial cells in the capillary plexus start differentiating into cells with arterial and venous identities.

Biomechanical factors and fluid dynamics have long been recognized as important regulators of angiogenesis. Thoma, a pioneer angiogenesis research, observed that within embryos, increases in local blood flow cause vessel diameters to enlarge, whereas decreases in local blood flow cause vessel diameters to shrink [10]. Chapman studied the angiogenesis of chicken embryos in which he removed the hearts and observed that the initial vessel patterns laid down during vasculogenesis remained undisturbed. He hypothesized that subsequent angiogenesis occurred by mechanical forces [11]. Murray proposed that vessel caliber is proportional to the amount of shear stress at the vessel wall [12].

Development of the Arterial System

After the heart starts circulating blood through the primitive vascular network, two aortas form at the dorsal region. Fusion starts in the middle section and then extends cranially and caudally; thus the single dorsal aorta develops (Fig. 2.1) [13, 14]. The dorsal aorta connects to the vitelline arteries in the mid portion and to the umbilical arteries in the caudal portion. In the cranial portion of the embryo, five pairs of aortic arches form sequentially at both sides. They originate from the aortic sac and connect to the ipsilateral dorsal aorta.

The layout of the primitive aortic arches is transformed to the adult aortic arch from week 6–8 of development. The first asnd second aortic arches exist only for a short period of time and then regress (Fig. 2.2a). The vertebral arteries form on the lateral side of the dorsal arteries and the intersegmental arteries connect between them horizontally. After the first and second aortic arches disappear, the segment of the dorsal aorta between the third

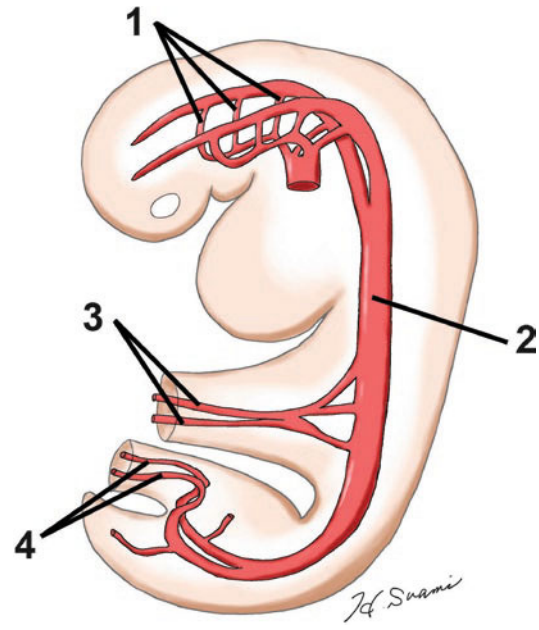

Fig. 2.1 Embryonic arteries at the fourth week of gestation (*1* aortic arches, *2* dorsal aorta, *3* vitelline arteries, and *4* umbilical arteries)

and fourth aortic arches regresses on both sides (Fig. 2.2b). The sixth pair of aortic arches forms from the aortic sac, and they give branches to the lung (Fig. 2.2c). A segment of only the right dorsal artery involutes between the bifurcation and the right seventh intersegmental artery. The pair of seventh intersegmental arteries elongates laterally; however other pairs of intersegmental arteries regress because of maturation of the vertebral arteries. The intermammary arteries derive from the seventh intersegmental arteries and extend caudally. The next involution occurs at the segment of the right sixth aortic arch between the right dorsal artery and pulmonary branch (Fig. 2.2d). The same segment of the left sixth aortic arch persists as the ductus arteriosus until the time of birth. The pulmonary trunk is separated from the aortic sac and with the sixth aortic arches. The seventh intersegmental arteries move cranially and elongate to limb buds to start supplying blood to the upper limbs.

In summary, the first and second aortic arches regress completely. The third aortic arches form a

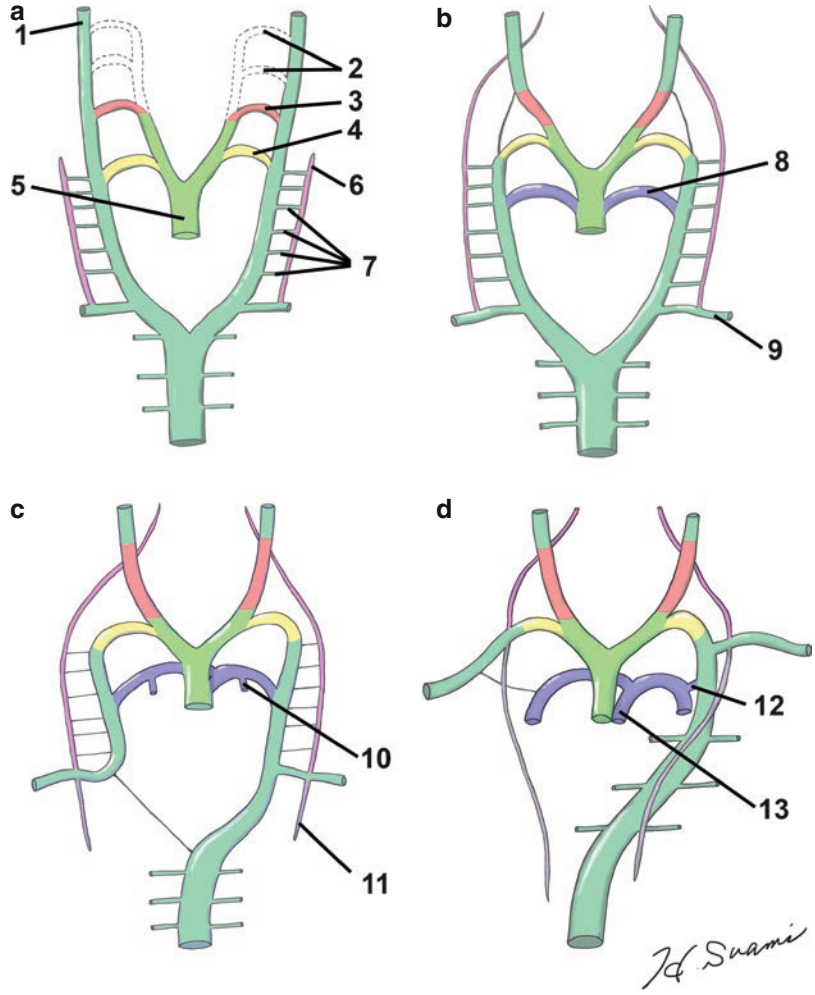

Fig. 2.2 Embryological development of the arterial system from the sixth to eighth week of gestation. (**a**) The first and second aortic arches exist only for a short period of time (*1* dorsal aorta, *2* the first and second aortic arches, *3* the third aortic arch, *4* the fourth aortic arch, *5* aortic sac, *6* vertebral artery, and *7* intersegmental arteries). (**b**) The sixth aortic arch forms from the aortic sac (*8* the sixth aortic arch and *9* the seventh intersegmental artery). (**c**) A segment of the right dorsal artery involutes between the bifurcation and the right seventh intersegmental artery (*10* pulmonary artery and *11* internal mammary artery). (**d**) A segment of the right sixth aortic arch involutes between the right dorsal artery and pulmonary brunch (*12* ductus arteriosus and *13* pulmonary trunk)

part of the carotid arteries. The fourth aortic arches form a part of the aortic arch and a part of the right subclavicular artery. The sixth aortic arches form the pulmonary arteries and the ductus arteriosus. The seventh intersegmental arteries form the subclavicular arteries.

Anomalous Development of the Aortic Arch

Due to the complex nature of the evolution and involution that occurs during the development of the major arteries, and the fact that multiple processes must occur correctly, anomalous conditions of the aortic arch can occur. For example, a patent ductus arteriosus is one of the most common abnormalities, occurring in around 8 out of 10,000 births [14]. Coarctation of the aorta is another one of the more commonly occurring at around 3.2 out of 10,000 births [14]. This abnormality is classified into two types: pre-ductal and post-ductal corresponding to the anatomic position of the lesion with the ductal arteriosus.

Abnormal involution and persistence of primitive arteries cause several other malformations. "Abnormal origin of the right subclavicular artery" occurs when the right fourth aortic arch and a part of the right dorsal artery cranial to the seventh intersegmental artery involute and the right dorsal artery caudal to the seventh intersegmental artery persists. "Double aortic arch" occurs when all parts of the right dorsal artery persist. "Interrupted aortic arch" occurs when both fourth aortic arches involute and the right dorsal artery caudal to the seventh intersegmental artery persists. Thus, knowledge of abnormal involution and persistence during the early stages of embryological development helps our understanding of the pathogenesis of congenital arterial malformations.

Development of the Venous System

The primitive vascular structure in capillary and reticular plexuses in the early embryonic stage soon develops distinguishable arteries and veins. The part of the body distal to the developing heart drains through paired anterior cardinal veins, whereas the caudal portion of the body drains through paired posterior cardinal veins (Fig. 2.3) [15].

In the fifth week, paired anterior cardinal veins and posterior cardinal veins form, and they are the first embryonic veins to drain the cerebral and caudal portion of the body, respectively. Soon, subcardinal veins sprout from the posterior cardinal veins (Fig. 2.4a) [4]. The following alterations occur over the fifth to seventh week. Paired supracardinal veins form from the posterior cardinal veins. The sub- and supracardinal veins anastomose on both sides to form the "subsupracardinal anastomoses" (Fig. 2.4b). The posterior cardinal veins regress because now subcardinal and supracardinal veins supersede them (Fig. 2.4c). Longitudinal segments of left subcardinal vein cranial to the subcardinal anastomosis also regress. Paired anterior cardinal veins form a new anastomosis to let the blood drain from the left anterior cardinal vein into the right anterior cardi-

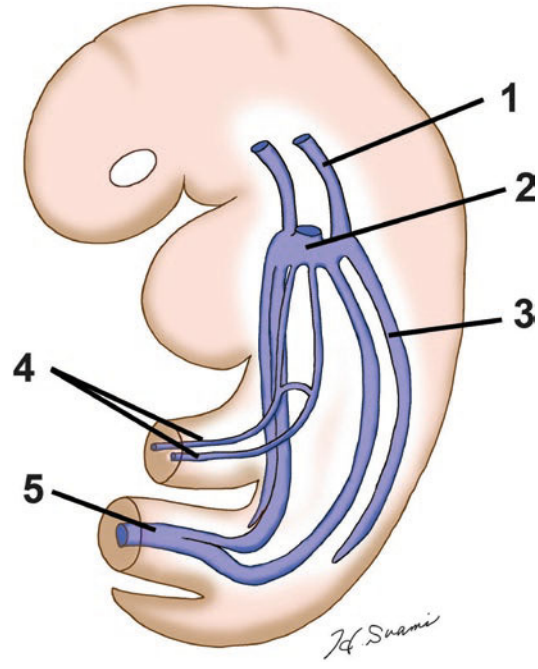

Fig. 2.3 Embryonic veins at the fourth week of gestation (*1* anterior cardinal vein, *2* sinus venosus, *3* posterior cardinal vein, *4* vitelline veins, and *5* umbilical vein)

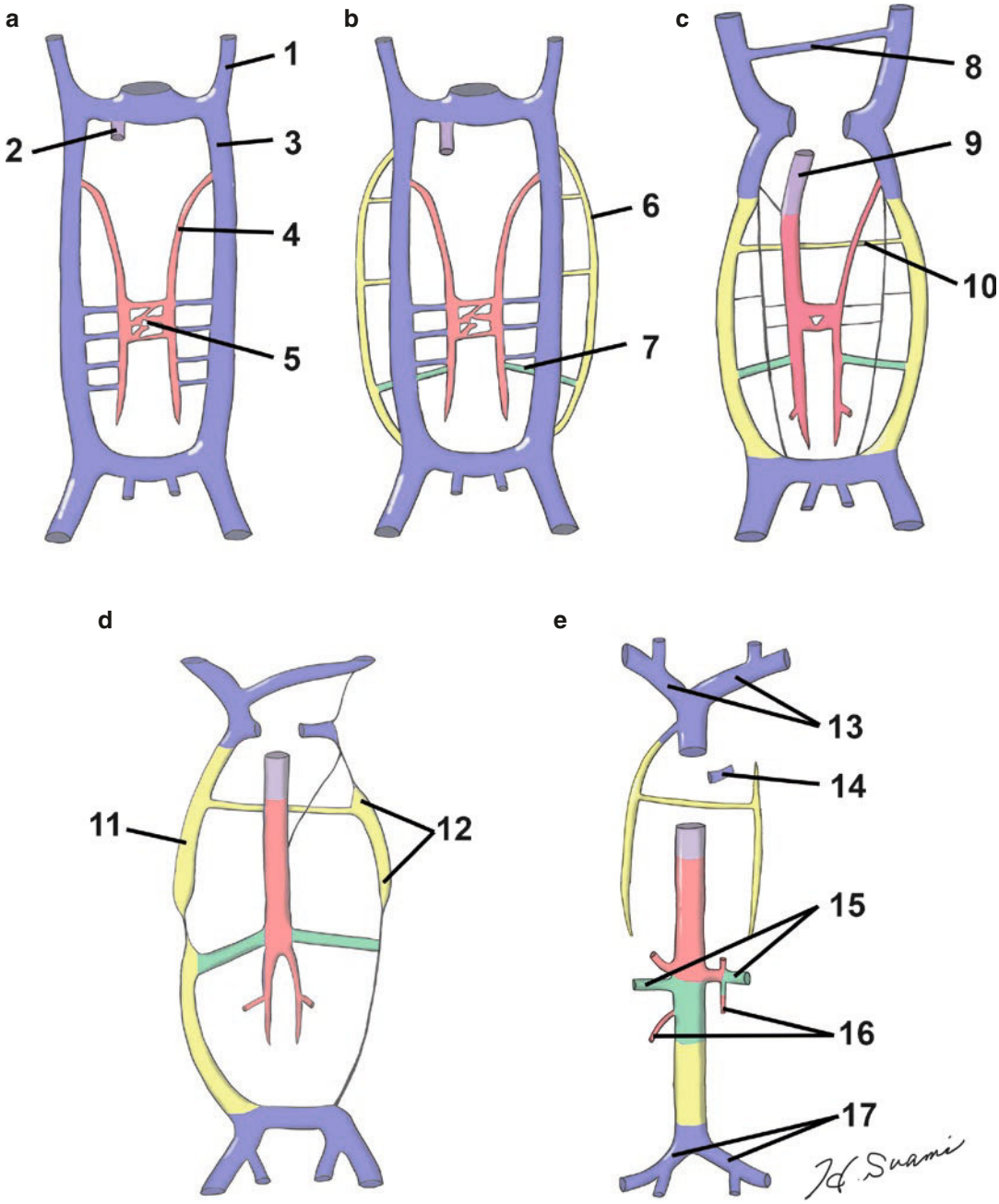

Fig. 2.4 Embryological development of the venous system from the fifth to seventh week of gestation. (**a**) The subcardinal veins form from the posterior cardinal veins (*1* anterior cardinal vein, *2* right vitelline vein, *3* posterior cardinal vein, *4* subcardinal vein, and *5* subcardinal anastomosis). (**b**) Paired supracardinal veins form from the posterior cardinal veins (*6* supracardinal vein and *7* subsupracardinal anastomosis). (**c**) The posterior cardinal veins regress. New anastomoses form between the anterior cardinal veins and between the posterior cardinal veins (*8* anastomosis between the anterior cardinal veins, *9* hepatic vein, and *10* anastomosis between the posterior cardinal veins). (**d**) Cranial part of the supracardinal veins remains as azygos, hemiazygos, and accessory hemiazygos veins (*11* azygos vein and *12* hemiazygos and accessory hemiazygos veins). (**e**) A right-sided inferior vena cava forms (*13* brachiocephalic veins, *14* coronary sinus, *15* renal veins, *16* spermatic or ovarian veins, and *17* common iliac veins)

nal vein via the newly formed "brachiocephalic vein." A new anastomosis forms between supracardinal veins. The right supracardinal vein remains as the "azygos vein" together with the cranial part of the right posterior cardinal veins forms the "arch of azygos vein," while the left supracardinal vein becomes the "hemiazygos vein" and also the "accessory azygos vein" (Fig. 2.4d). Most of the veins on the left side regress, resulting in a right-sided "inferior vena cava" (IVC), to meet the new conditions to be faced upon birth (Fig. 2.4e). The portion of the left anterior cardinal vein caudal to the brachicephalic anastomosis regresses, and it transforms into the "oblique vein" of the left atrium (vein of Marshall) on the back of the left atrium and the "coronary sinus." The right anterior cardinal vein forms the superior vena cava (SVC) [16].

Anomalous Development of the Superior and Inferior Vena Cava

Due to the complex evolutional process to form the SVC, from various segments of three different embryonic/cardinal veins, there is a high risk of defective development of the SVC. In addition, there are various conditions of the stenosis or dilatation and/or aneurysm formation, either with or without internal defect. "Double superior vena cava" is the outcome of the persistence of the left caudal anterior cardinal vein [17]. It is due to the failed degeneration and/or involution of the left anterior cardinal vein proximal to brachiocephalic anastomosis. Left SVC is the outcome that results from persistence of the entire left cardinal vein. In the absence of the right proximal superior vena cava, the blood from the right upper body drains to the "left SVC" via right brachiocephalic vein.

There is a high risk of developmental anomalies arising as a result of errors of the IVC developmental process. "Absence of the suprarenal inferior vena cava" (IVC) may arise as a result of the complexity of fusion process of multiple blocks of three different cardinal veins, which needs to occur to meet the new conditions following birth [18]. It occurs when the right subcardinal vein fails to make a connection with the liver. The IVC drains into the arch of the azygos and the hepatic veins drain independently to the right atrium. "Double inferior vena cava" occurs when iliac anastomosis of the postcardinal vein regresses or shrinks and the left subcardinal vein, caudal to anastomosis of the subcardinal veins, persists to maintain drainage from the left iliac veins [19].

Development of the Lymphatic System

Development of the human lymphatic system begins in the sixth or seventh week of embryogenesis following development of the primitive vascular system. First, paired jugular lymph sacs, which originate from the anterior cardinal veins, develop near the junction of the subclavicular and internal jugular veins [5, 6]; lymphatic capillaries and vessels sprout centrifugally toward the head and neck, upper extremities, and upper torso. Each jugular sac maintains connection to the subclavicular vein. Secondary to this, the retroperitoneal lymph sac derives from the mesonephric veins and lies in the root of the mesentery. The sac forms visceral lymphatic vessels including the thoracic duct. The retroperitoneal sac joins the cisterna chili and they drain into the thoracic duct. Initially, two thoracic ducts form connecting the jugular sacs and the cisterna chili. Anastomoses form between them. The single thoracic duct develops from the cranial left thoracic duct, the anastomosis, and the right distal thoracic duct. Lastly, paired posterior lymph sacs develop near the junctions of the primitive iliac veins and posterior cardinal veins. The lymphatic vessels from these sacs spread toward the lower torso and lower extremities (Fig. 2.5).

Anomalous Development of the Lymphatic System

Lymphatic malformations often manifest clinically as congenital or heredity lymphedema resulting from insufficient development of the

lymphatic system during the late stages of embryological development. Lymphatic congenital defects present in various forms, including hypoplastic, hyperplastic, or aplastic lesions of the lymphatic vessels and/or lymph nodes. Such lesions are associated with malfunctions of the lymphatic system.

Truncular lymphatic malformations do not always result in an evident morphological defect of the lymphatic system, however. For example, patients with "Milroy-Meige syndrome," or inherited primary lymphedema, which occurs right after birth, do not have any apparent structural defects of the lymphatic system but rather have functional impairment at the capillary lymphatic or initial lymphatic level [20]. In addition, patients with "lymphedema-distichiasis syndrome" have impairment of the endoluminal valves, which causes lymphatic reflux. The syndrome is associated with other clinical symptoms including cardiac malformations, cleft palate, ptosis, double eyelashes, and yellow nails.

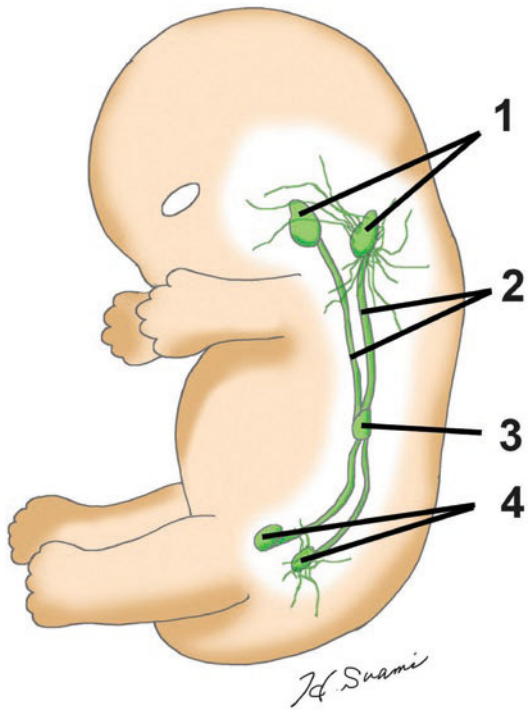

Fig. 2.5 Embryonic lymphatics at the seventh week of gestation (*1* jugular lymph sacs, *2* thoracic ducts, *3* retroperitoneal lymph sac, and *4* posterior lymph sacs)

Summary

Embryological development of the vascular system is an intricate sequential process involving evolution, involution, generation, and degeneration. Anomalous involution often triggers formation of abnormal circulation that then requires and promotes persistence of the primitive vascular structure. Congenital vascular malformations demonstrate a wide variety of clinical manifestations in terms of not only their pathological presentation but also their response to therapy. Understanding the embryological background of these lesions, which also relates to their clinical prognoses, is fundamental to comprehending dynamic circulatory alterations following treatment.

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Part II

Pathogenesis of Congenital Vascular Malformation (CVM)

Angiogenesis and Vascular Malformations

3

Patricia E. Burrows

In the process of vasculogenesis, blood and lymphatic channels form in the embryo from clusters of angioblasts that differentiate into endothelium and other mesenchymal cells that form the vessel wall [smooth muscle cells, fibroblasts] and surrounding mesenchyme. Early vascular channels form the primary vascular plexus and vascular remodeling leads to development of arteries, veins, and capillaries. Subsequently, new blood vessels form from sprouting, intussusceptive vascular growth, and splitting of vessels from preexisting channels. Specification is believed to be related to expression of Efrin B2 in arterial and EphB2 in venous endothelium. Lymphatic channels form from veins. Defects in any of the proteins involved in the regulation of vasculogenesis and angiogenesis can result in abnormal channels that can subsequently expand and cause symptoms. After birth, abnormal regulation of angiogenesis can lead to increased cell proliferation or reduced apoptosis, thrombosis, and other changes that contribute to the clinical manifestations of a vascular malformation. Congenital vascular malformations, in general, enlarge in proportion to the growth of the affected child, but it is well known that they may expand episodically, especially during periods of accelerated somatic growth and increased hormonal stimulation. The recent finding that endothelial cells in vascular malformations have increased receptors to human growth hormone and somatostatin compared with those in normal tissue explains the increased growth and symptomatology of vascular malformations that is seen during growth spurts as well as at puberty and during pregnancy [1, 2]. In addition, animal models have confirmed the responsiveness of vascular malformations to angiogenic growth factors [3].

Venous Malformations

Familial mucocutaneous venous malformations and 50 % of sporadic VM are caused by mutations in the tyrosine kinase receptor TIE2. Experiments show that in human endothelial cells, mutant tie2 and its ligands, angiopoietins 1 and 2, cause increased activation of AKT signaling and reduced production of platelet-derived growth factor-B, which is important in mural cell recruitment. These molecular changes, both in the lab setting and in humans, cause VMs characterized by a defective endothelial cell monolayer, deficient smooth muscle in the vessel wall, and defects in thrombospondin function, while abnormalities result in formation of enlarged, disfigured, and fragile venous channels, as well as intralesional thrombosis and clotting protein consumption [4]. The cause and effect of TIE2

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mutation in the etiology of VM is supported by the observation that treatment of patients with sirolimus, which suppresses AKT, appears to control the growth and improve the consumption coagulopathy of extensive VM [5]. Rapid recurrence of symptomatic VM after partial resection is common, presumably due to stimulation of venous angiogenesis. In a similar fashion, even after effective endovascular ablation of malformed venous channels, similarly abnormal channels, presumably collaterals, can develop in the adjacent soft tissue. Intralesional thrombi created by sclerotherapy can be recanalized by circulating endothelial progenitor cells, leading to new abnormal channels. This is the reason that sclerotherapy should be repeated until the vessel is occluded permanently by fibrosis.

Abnormal angiogenesis can also occur in veins without TIE2 mutation. Angiogenesis in a partly thrombosed vein can lead to development of a focal vascular mass termed Masson's tumor. Arteriovenous shunts can develop in the walls of partly occluded veins after venous thrombosis, or after incomplete endovascular ablation (Fig. 3.1). In fact, dural sinus thrombosis is believed to be the trigger for development of acquired dural AVMs in adults.

Arteriovenous Malformations [AVMs]

AVMs are also caused by abnormal regulation of blood vessel development. More than 860 genes are known to be upregulated or downregulated in cerebral AVMs [6]. The study of familial forms of AVM has revealed a number of causative genetic mutations, including ENDOGLIN (ENG), ACTIVIN RECEPTOR-LIKE KINASE 1 [ALK1], and SMAD4 in patients with hereditary hemorrhagic telangiectasia [HHT], RASA1 in patients with capillary malformation-arteriovenous

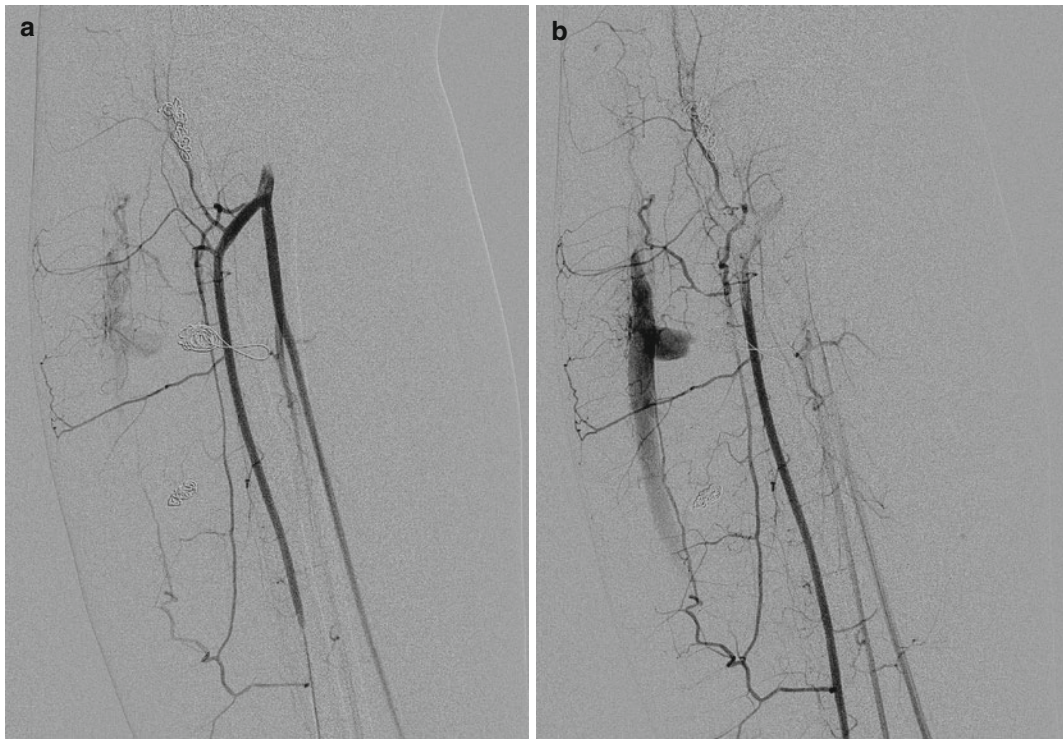

Fig. 3.1 Angiogenesis causing acquired arteriovenous fistulae in the wall of a marginal vein after unsuccessful endovenous laser treatment. Probable triggers: injury and hypoxia. (**a**, **b**) Sequential images from a right anterior tibial angiogram showing tiny arteriovenous shunts into the distal segment of the partly occluded vein

malformation [CM-AVM], and PTEN in patients with AVM associated with Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome. A number of animal models have been developed, mainly by creating mutations in endoglin (eng), activin receptor-like kinase 1 [Alk1], RASA1, and notch pathways [7–9]. In the lab setting, angiogenesis in normal and abnormal endothelial cell models can be stimulated by vascular endothelial growth factors (VEGF). In the Alk1 mouse model, AVMs establish from newly formed arteries and veins, rather than from remodeling of a preexistent capillary network. Creation of a wound or stimulation with VEGF is needed to create the AVM in ALK1-deficient adult mice. In this model, VEGF blockade can prevent the formation of AVM and arrest the progression of AVM development [10]. Clinically, most AVMs evolve over time, and it has been known for many years that quiescent lesions can become more active [increased shunting, swelling, pain] during periods of active somatic growth and as a result of conditions that are known to upregulate vascular growth factors, such as surgery, embolization, trauma, inflammation, puberty, and pregnancy (Figs. 3.2 and 3.3). Histochemistry of resected AVM tissue has revealed increased numbers of endothelial cell receptors for human growth factor and somatostatin, as well as upregulation of MMP9, inflammatory markers, and VEGF [11]. Recently, it has been found that suppression of VEGF pharmacologically [bevacizumab and thalidomide] can result in decreased arteriovenous shunting and improved symptomatology in some patients with HHT [12]. Doxycycline appears to decrease cerebral MMP-nine activity and angiogenesis induced by VEGF. Endothelial cells from resected AVMs respond to doxycycline and minocycline in cell culture, but clinical response in patients with symptomatic AVMs has not been well documented. One child with sporadic AVM had an excellent, dose-dependent, sustained response to treatment with marimastat, a preclinical broad-spectrum MMP inhibitor. Other patients with AVMs have been treated with angiogenesis inhibitors anecdotally, but, aside from a small trial of minocycline in patients with cerebral AVMs, there have not been any prospective clinical trials.

While it has been widely believed that AVMs are congenital, there is increasing evidence that AVMs can be acquired [13]. Triggers for postnatal development of AVM include venous thrombosis [deep vein thrombosis in the lower extremities and dural sinus thrombosis resulting in dural AVM], ischemia [e.g., cerebral infarct], and trauma [e.g., chronic posttraumatic AV fistula, uterine AVMs]. While the mechanisms leading to acquired AVM have not been studied in detail, the presence of increased numbers of endothelial progenitor cells in thrombosed blood vessels as well as higher grade AVMs suggests a role for these cells, likely in response to upregulation of vascular growth factors [11, 14].

Summary

Vasculogenesis, normal and aberrant angiogenesis, and pathological angiogenesis stimulated by extrinsic factors are all involved in development and progression of vascular malformations. Antiangiogenic drug treatment appears to be effective in controlling the development and progression of AVM in animal models as well as in patients with HHT, who have mutations in ALK1 and ENG. Further study of patients with sporadic AVM and patients with VM will hopefully lead to effective pharmacotherapy in the future.

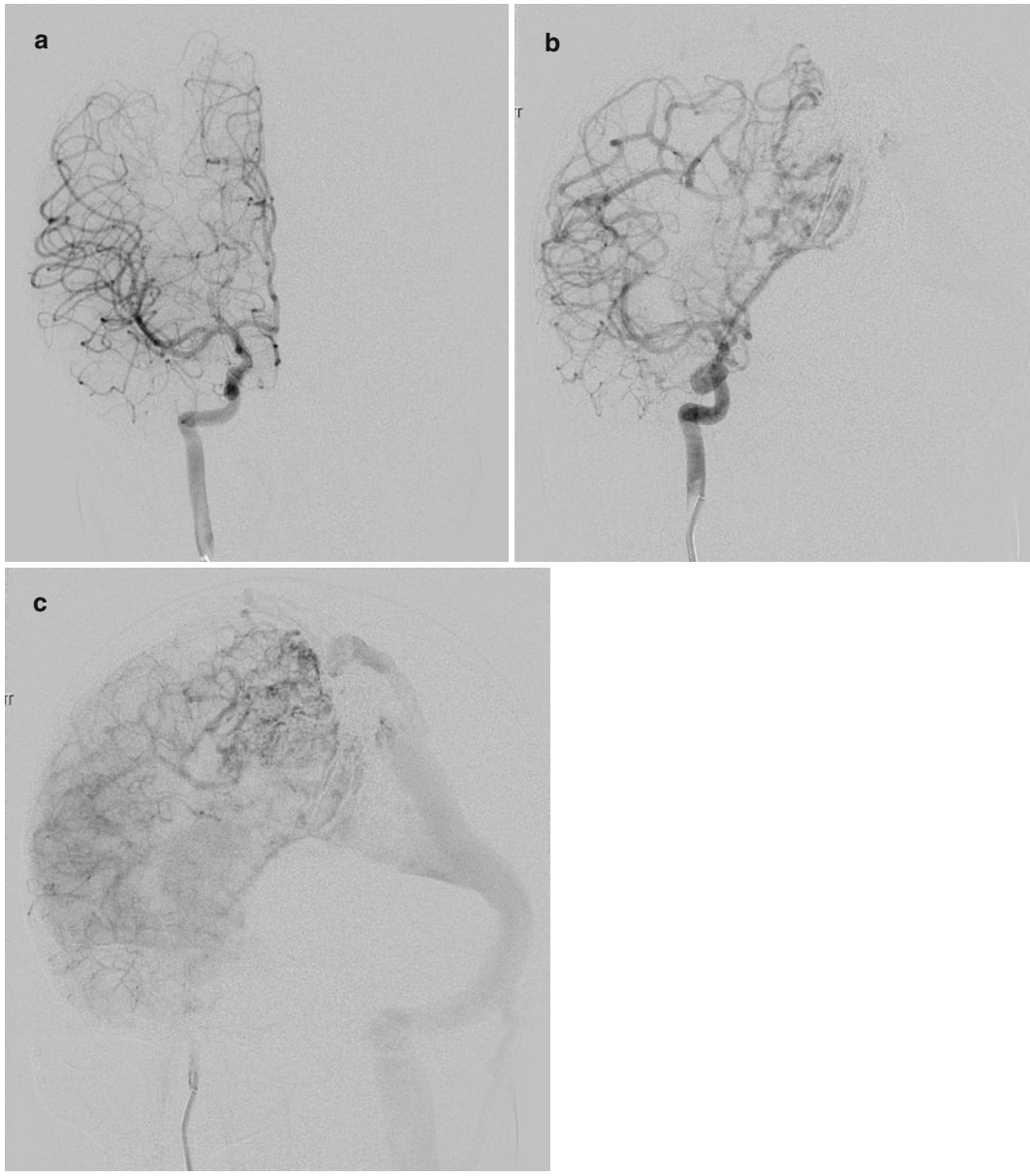

Fig. 3.2 Stimulated angiogenesis in an 11-year-old girl with dural AVM, most likely triggered by somatic growth, embolization, and onset of puberty. (**a**) *Right* internal carotid angiogram, frontal projection in 2008, showing no arteriovenous shunting. (**b**, **c**) *Right* internal carotid arteriogram, frontal oblique projection, shows multiple new arteriovenous fistulae between pial branches of the anterior and middle cerebral arteries and the superior sagittal sinus. In the interval, the patient had undergone additional embolization of the dural AVM and started her menstrual cycles

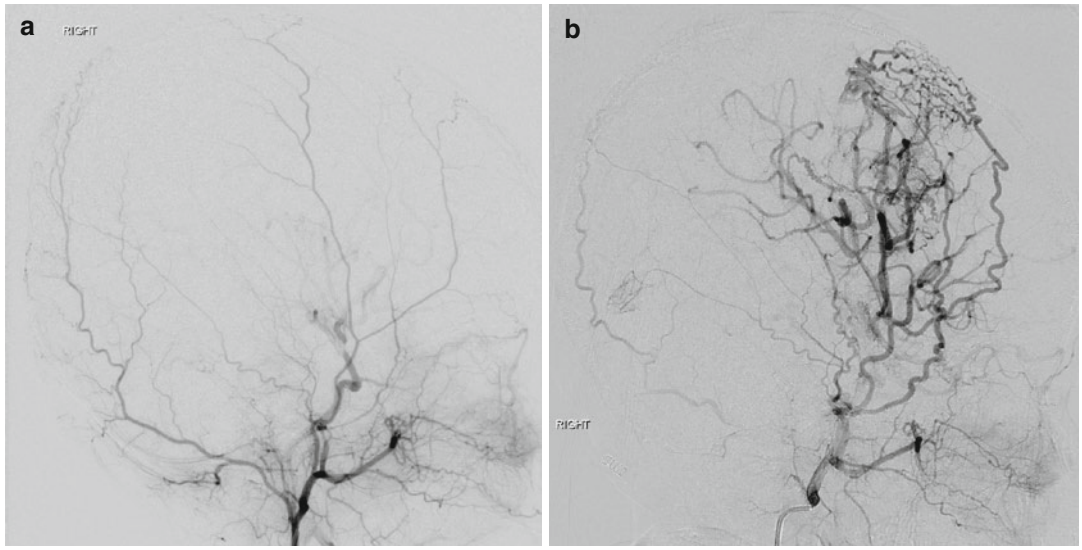

Fig. 3.3 Angiogenesis in a one-year-old girl with severe stenosis of the right internal carotid artery treated by synangiosis surgery. Probable stimuli: ischemia, hypoxia, surgical trauma, and somatic growth. (**a**) *Right* external carotid arteriogram, lateral projection prior to surgery shows normal size and distribution of the external carotid artery branches. (**b**) *Right* external carotid angiogram 1 year after synangiosis shows increased size and tortuosity of the superficial temporal artery with extensive anastomoses with the right middle cerebral artery branches

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Genetic Aspects of Vascular Malformations

4

Francine Blei

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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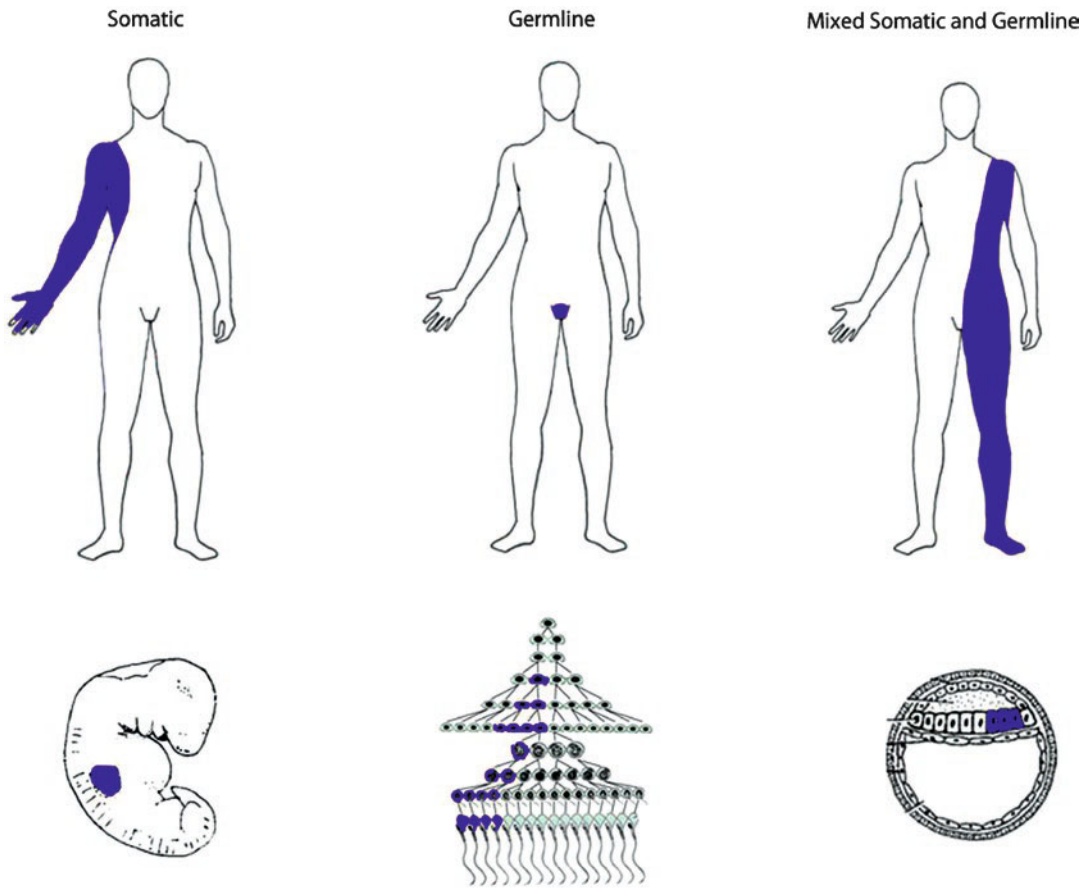

Fig. 4.1 Mosaicism and clinical genetics: This figure shows possible distributions of a mutation in adults with purely somatic, purely germline, or mixed somatic and germline patterns along the top row. The bottom figures demonstrate possible mutation patterns in the late embryo, during spermatogenesis, 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,