

Klippel-Trenaunay-Weber Syndrome

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1. Core Definition

Klippel-Trenaunay-Weber syndrome (KTWS), often historically referred to and frequently conflated with **Klippel-Trenaunay syndrome** (KTS), represents a complex, rare congenital vascular anomaly primarily characterized by a triad of distinct clinical features. This condition, also known by alternative designations such as angioosteohypertrophy syndrome and hemangiectatic hypertrophy, involves malformations of vascular and lymphatic systems, typically presenting at birth or shortly thereafter. The hallmark symptoms include a **port-wine stain** (a capillary malformation), **varicose veins** or venous malformations, and **hypertrophy** (overgrowth) of soft tissues and bone, most commonly affecting a limb. While the term KTWS specifically implies the presence of arteriovenous malformations (AVMs), which are not typically found in KTS, the nomenclature has evolved significantly, leading to complexities in diagnosis and classification.

The syndrome is generally considered a sporadic condition, meaning it occurs randomly and is not typically inherited from parents. Its manifestations can vary widely in severity, ranging from mild cosmetic concerns to debilitating functional impairments and life-threatening complications. The characteristic overgrowth can lead to substantial discrepancies in limb size, sometimes resulting in **gigantism** of the affected extremity, though in rare instances, hypotrophy (underdevelopment) may also be observed. Beyond the classic triad, patients may experience a spectrum of other health issues, particularly involving the **lymphatic system**, which can contribute to chronic pain, swelling, and increased risk of infection. Effective management relies on a multidisciplinary approach focused on alleviating symptoms and preventing complications, as a definitive cure remains elusive.

2. Etymology and Historical Development

The initial description of the syndrome now widely known as **Klippel-Trenaunay syndrome** (KTS) dates back to 1900, when French physicians **Maurice Klippel** and **Paul Trenaunay** published their observations on a congenital condition characterized by a port-wine stain, varicose veins, and limb hypertrophy. Their work provided the foundational understanding of this distinct clinical entity, highlighting the unique combination of vascular and musculoskeletal abnormalities. This seminal description laid the groundwork for future research and classification efforts within the realm of vascular anomalies.

The "Weber" addition to the syndrome's name emerged seven years later when German-British physician **Frederick Parkes Weber** described similar but not identical cases in 1907 and again in

1918. Weber's cases presented with similar features to those described by Klippel and Trenaunay but importantly included the presence of **arteriovenous malformations** (AVMs), which are direct connections between arteries and veins that bypass the capillary beds. This distinction, though subtle, was critical because AVMs introduce different hemodynamic challenges and potential complications compared to purely venous or lymphatic malformations. For a period, conditions exhibiting AVMs in addition to the Klippel-Trenaunay triad were designated as **Klippel-Trenaunay-Weber syndrome** (KTWS), recognizing Weber's contribution to identifying this more complex variant.

Over time, as diagnostic capabilities improved and understanding of vascular biology advanced, the classification of these syndromes became more refined. The inclusion of AVMs in Weber's descriptions led to the eventual re-evaluation of KTWS as potentially distinct from KTS. Modern medical consensus often differentiates KTS (lacking AVMs) from **Parkes Weber syndrome** (PWS), where AVMs are a defining feature. Consequently, the term Klippel-Trenaunay-Weber syndrome has largely fallen out of favor in precise medical terminology, with cases previously categorized under KTWS now typically reclassified as either KTS (if AVMs are absent) or PWS (if AVMs are present). This evolution in nomenclature reflects a growing precision in defining these complex conditions, moving towards classifications based on underlying pathology rather than purely phenotypic similarities.

3. Clinical Manifestations: The Classic Triad

The diagnostic foundation of **Klippel-Trenaunay-Weber syndrome**, and indeed Klippel-Trenaunay syndrome, rests upon the recognition of a characteristic clinical triad, though the severity and completeness of these features can vary. The first component is the **port-wine stain**, or capillary malformation. This is typically a flat, pink to purplish-red birthmark that appears on the skin, often present at birth. While it can occur anywhere on the body, in KTWS/KTS, it usually affects the limb that also exhibits hypertrophy, following a dermatomal distribution. Over time, these lesions may darken, thicken, and develop nodularity, potentially leading to bleeding or chronic irritation. The aesthetic impact can be significant, but more importantly, extensive lesions can be indicative of underlying vascular anomalies.

The second essential feature is the presence of **varicose veins** or more broadly, venous malformations. Unlike common varicose veins that primarily affect superficial leg veins, those associated with KTWS/KTS often appear in unusual locations, such as the lateral aspect of the thigh or trunk, and can involve deep venous systems. These venous anomalies are characterized by abnormally dilated, tortuous, and poorly functioning veins, often presenting as bluish, bulging vessels beneath the skin. Complications can include chronic venous insufficiency, recurrent bleeding, superficial **thrombophlebitis** (inflammation with clot formation), and even deep vein thrombosis. The impaired venous return can significantly contribute to the limb swelling and pain

experienced by affected individuals.

The third and often most functionally impactful component of the triad is **hypertrophy**, or overgrowth, of soft tissues and bone. This typically affects the same limb as the port-wine stain and varicose veins, though it can occasionally manifest in other body parts. The hypertrophy can result in substantial limb length and girth discrepancies, leading to conditions like macrodactyly (enlarged digits) or overall **gigantism** of the entire limb. This overgrowth can cause significant functional limitations, gait disturbances, chronic pain, and orthopedic problems such as **scoliosis** or joint deformities. In rare cases, hypotrophy (underdevelopment) of the affected limb may also occur, although less frequently than overgrowth. The severity of hypertrophy dictates much of the orthopedic management required throughout a patient's life.

4. Associated Features and Complications

Beyond the classic triad, individuals with **Klippel-Trenaunay-Weber syndrome** can experience a wide array of associated features and complications, underscoring the systemic nature of the vascular and lymphatic malformations. One significant area of involvement is the **lymphatic system**. Patients frequently develop **lymphedema**, a chronic swelling caused by impaired lymphatic drainage, which exacerbates the limb hypertrophy and can lead to recurrent cellulitis and skin breakdown. More severe lymphatic anomalies can manifest as **chylous effusions** in the chest (chylothorax) or abdomen (chylous ascites), or as internal **lymphatic malformations** that can affect various organs.

The presence of **arteriovenous malformations** (AVMs) is a critical distinguishing factor historically associated with the "Weber" designation. While AVMs are typically absent in pure Klippel-Trenaunay syndrome, their inclusion in cases termed KTWS indicates a more complex vascular anomaly with direct shunting of arterial blood into the venous system. These AVMs can lead to high-output cardiac failure, bleeding, and ischemia in distal tissues due to "steal" phenomena. Furthermore, patients are at an elevated risk for **thromboembolic events**, including deep vein thrombosis and potentially pulmonary embolism, due to stasis in the venous malformations and possible underlying coagulopathies.

Other less common but significant complications can affect various organ systems. Skeletal abnormalities extend beyond simple hypertrophy and may include **scoliosis**, joint contractures, and foot deformities, requiring extensive orthopedic management. Gastrointestinal involvement, such as vascular malformations in the bowel, can lead to chronic bleeding, anemia, and protein-losing enteropathy. Similarly, genitourinary vascular anomalies can cause hematuria or bladder dysfunction. Ocular involvement, including glaucoma or retinal vascular anomalies, can also occur, necessitating regular ophthalmic surveillance. The widespread potential for complications highlights the need for comprehensive, interdisciplinary medical care throughout the patient's life.

5. Pathophysiology and Genetics

The underlying genetic basis for both **Klippel-Trenaunay syndrome** (KTS) and similar vascular overgrowth syndromes, including those historically grouped under **Klippel-Trenaunay-Weber syndrome** (KTWS), has been increasingly elucidated in recent years. The primary genetic culprit identified in a significant proportion of these cases is a somatic mosaic mutation in the **PIK3CA gene**. Somatic mosaicism means that the mutation occurs after conception in a developing embryo, affecting only a subset of cells, rather than being inherited through germline cells. This explains why the condition is typically sporadic and not passed down from parents to offspring. The distribution of affected cells dictates the extent and location of the clinical manifestations.

The **PIK3CA gene** encodes the p110 α catalytic subunit of phosphatidylinositol 3-kinase (PI3K), a crucial enzyme involved in the PI3K/AKT/mTOR signaling pathway. This pathway is a master regulator of cell growth, proliferation, survival, and differentiation. When a somatic activating mutation occurs in PIK3CA, it leads to constitutive activation of this pathway in the affected cells. This uncontrolled signaling results in abnormal cell growth and proliferation, particularly in the endothelial cells lining blood and lymphatic vessels, as well as in stromal cells. This hyperactive pathway drives the development of the characteristic vascular malformations (capillary, venous, lymphatic) and the localized tissue overgrowth (hypertrophy) seen in the syndrome.

The spectrum of disorders caused by activating PIK3CA mutations is now collectively referred to as **PIK3CA-Related Overgrowth Spectrum** (PROS). This umbrella term encompasses various conditions, including KTS, **hemimegalencephaly**, fibroadipose overgrowth (FAO), and others, all sharing the common molecular etiology of PIK3CA somatic mutations. The specific phenotype observed in an individual depends on the timing of the mutation during development, the type of cells affected, and the specific mutation variant. While KTS is a well-established entity within PROS, the historical KTWS, which included AVMs, is now often molecularly linked to conditions like **Parkes Weber syndrome**, which also involves PIK3CA mutations but manifests with arteriovenous shunting due to specific patterns of PI3K pathway activation.

6. Diagnosis

The diagnosis of **Klippel-Trenaunay-Weber syndrome**, and its contemporary counterparts like Klippel-Trenaunay syndrome, is primarily clinical, based on the presence and recognition of the characteristic triad of symptoms. A thorough physical examination is paramount, assessing the extent and distribution of the port-wine stain, palpating for abnormal venous structures, and measuring limb circumference and length to identify hypertrophy. The history typically reveals the presence of these features from birth or early infancy, and the progression of symptoms such as swelling, pain, or bleeding provides crucial diagnostic clues. However, due to the variability in presentation and the potential for incomplete triads, imaging studies are essential to confirm the

diagnosis, delineate the full extent of the anomalies, and rule out other conditions.

Various imaging modalities are employed to characterize the vascular and soft tissue malformations. **Doppler ultrasound** is often the first-line investigation for evaluating venous malformations, assessing blood flow patterns, and identifying areas of venous stasis or reflux. **Magnetic Resonance Imaging** (MRI) and Magnetic Resonance Angiography (MRA) are invaluable for detailed anatomical mapping of the extent of soft tissue and bone hypertrophy, as well as for characterizing venous, lymphatic, and especially arteriovenous malformations (if present, distinguishing it towards Parkes Weber syndrome). These modalities provide excellent soft tissue contrast, allowing for the visualization of deep-seated anomalies not apparent on the surface. **Lymphoscintigraphy** may be performed to assess lymphatic function and confirm the presence of lymphedema or lymphatic malformations. Plain radiographs can help evaluate bone hypertrophy and identify associated orthopedic issues like scoliosis or limb length discrepancy.

While clinical and imaging findings are usually sufficient for diagnosis, **genetic testing** for somatic PIK3CA mutations is increasingly used to confirm the diagnosis and classify the condition within the broader **PIK3CA-Related Overgrowth Spectrum** (PROS). This molecular confirmation can be particularly useful in atypical presentations or when differentiating KTWS/KTS from other similar vascular anomalies, such as **Proteus syndrome** or **Bannayan-Riley-Ruvalcaba syndrome**. Furthermore, genetic diagnosis can guide targeted therapies, such as **sirolimus**, which directly targets the PI3K/AKT/mTOR pathway. Differential diagnosis must carefully consider **Parkes Weber syndrome**, which shares many features but is definitively characterized by the presence of high-flow arteriovenous malformations, in contrast to the predominantly low-flow malformations of Klippel-Trenaunay syndrome.

7. Management and Treatment Strategies

The management of **Klippel-Trenaunay-Weber syndrome**, encompassing its various manifestations, is complex, lifelong, and requires a highly individualized, multidisciplinary approach. Given that there is currently no definitive cure, treatment strategies are primarily focused on symptomatic relief, prevention of complications, and optimization of function and quality of life. The core principle involves addressing each component of the syndrome and its associated features with appropriate medical, surgical, and interventional therapies. Due to the rarity and complexity of the condition, management is best conducted at specialized centers with expertise in vascular anomalies.

Specific treatments target the individual components of the syndrome. For the **capillary malformation**, **pulsed dye laser therapy** is the mainstay, aiming to lighten the birthmark and reduce its thickening, though multiple sessions are often required and complete eradication is rare. **Venous malformations** and varicose veins are managed through a combination of conservative

and interventional methods. Compression garments are essential for reducing swelling and supporting venous return. **Sclerotherapy**, involving the injection of a sclerosant agent into the malformation to induce fibrosis, is frequently employed. Surgical excision of superficial varicose veins or complex venous malformations may be necessary, especially for symptomatic lesions or those prone to bleeding or thrombosis. Deep venous system involvement often precludes extensive surgical intervention, emphasizing conservative management.

The **limb hypertrophy** and associated **lymphedema** demand comprehensive orthopedic and lymphatic management. Compression therapy using bandages or custom-fitted garments is crucial for controlling swelling and preventing further enlargement. Physical therapy, including manual lymphatic drainage and exercise, helps reduce edema and improve mobility. For significant limb length discrepancy, orthopedic surgical interventions such as **epiphysiodesis** (growth plate arrest) in the longer limb, or **limb shortening/lengthening procedures**, may be performed to improve gait and function. In cases with intractable lymphedema, debulking surgeries or lymphaticovenous anastomoses may be considered, though results can vary. For cases with arteriovenous malformations, as historically described in KTWS, embolization by interventional radiologists is often the preferred treatment to reduce blood flow and prevent complications like heart failure or limb ischemia. Furthermore, in light of the genetic discoveries, targeted pharmacological therapies like **sirolimus** (rapamycin), an mTOR inhibitor, have shown promise in reducing the size and improving symptoms of various **PIK3CA-Related Overgrowth Spectrum** (PROS) conditions, including KTS, by modulating the overactive PI3K/AKT/mTOR pathway.

8. Prognosis and Quality of Life

The prognosis for individuals with **Klippel-Trenaunay-Weber syndrome** is highly variable, depending significantly on the extent and severity of the vascular and lymphatic malformations, as well as the presence and successful management of complications. With appropriate and diligent medical care, many individuals can lead relatively normal lives, though they often face lifelong challenges requiring ongoing management. Early diagnosis and intervention are crucial for optimizing outcomes and preventing the progression of debilitating complications.

While the condition is not typically life-threatening in itself, associated complications can pose serious risks. These include chronic pain, recurrent infections (e.g., cellulitis in lymphedematous limbs), bleeding from fragile vascular lesions, and **thromboembolic events** such as deep vein thrombosis or pulmonary embolism. High-flow arteriovenous malformations (if present, aligning with Parkes Weber Syndrome) carry the additional risk of high-output cardiac failure. These complications can significantly impact morbidity and may necessitate emergency medical interventions, contributing to a reduced quality of life if not effectively managed.

Beyond the physical symptoms, the cosmetic impact of the port-wine stain and the functional

limitations imposed by limb hypertrophy and lymphedema can have profound psychosocial effects. Patients may experience body image issues, social stigma, and psychological distress, affecting their self-esteem and participation in daily activities. Therefore, comprehensive care must extend beyond purely medical interventions to include psychological support, counseling, and patient education. Despite these challenges, ongoing research, including the development of targeted therapies for PIK3CA-related conditions, offers increasing hope for improved management and a better long-term outlook for individuals affected by this complex syndrome.

9. Nomenclature and Distinctions

The nomenclature surrounding **Klippel-Trenaunay-Weber syndrome** (KTWS) has been a source of considerable confusion and ongoing debate within the medical community. Historically, the term KTWS was used to describe cases that presented with the classic Klippel-Trenaunay triad (port-wine stain, varicose veins/venous malformations, and limb hypertrophy) but also included **arteriovenous malformations** (AVMs). This distinguished it from Klippel-Trenaunay syndrome (KTS), which was defined by the absence of AVMs and was considered a purely low-flow vascular anomaly. Frederick Parkes Weber's observations of cases with AVMs led to his name being appended, recognizing these more complex presentations.

However, with advancements in understanding the pathophysiology and genetics of vascular anomalies, particularly the role of somatic PIK3CA mutations, the distinction has become clearer and the terminology more precise. The prevailing modern consensus among vascular anomaly specialists is to differentiate KTS from **Parkes Weber syndrome** (PWS). KTS is now strictly defined by the presence of the triad and the absence of AVMs, making it a low-flow mixed vascular malformation. In contrast, PWS is characterized by the presence of the triad along with definitive high-flow AVMs. This means that cases previously designated as Klippel-Trenaunay-Weber syndrome are now typically reclassified as Parkes Weber syndrome if AVMs are confirmed, or as Klippel-Trenaunay syndrome if AVMs are definitively absent.

This evolution in classification is not merely semantic; it reflects crucial differences in clinical management, prognosis, and underlying genetic mechanisms. High-flow AVMs, characteristic of PWS, carry distinct risks such as high-output cardiac failure and potential for severe hemorrhage, requiring different diagnostic and therapeutic approaches (e.g., embolization) compared to the predominantly venous and lymphatic issues in KTS. Both KTS and PWS, along with other similar conditions, are now recognized as part of the broader **PIK3CA-Related Overgrowth Spectrum** (PROS), unified by their common somatic activating mutations in the PIK3CA gene. This contemporary understanding aims to provide a more accurate diagnosis and guide more targeted, effective treatments for affected individuals, moving away from potentially imprecise historical designations like Klippel-Trenaunay-Weber syndrome.

Further Reading

[Klippel-Trénaunay Syndrome - Wikipedia](#)

[Parkes Weber Syndrome - Wikipedia](#)

[PIK3CA-Related Overgrowth Spectrum \(PROS\) - Children's Hospital of Philadelphia](#)

[PIK3CA gene - MedlinePlus Genetics](#)

[Mosaicism - Wikipedia](#)

[Port-wine stain - Wikipedia](#)

[Varicose veins - Wikipedia](#)

[Hypertrophy - Wikipedia](#)

[Lymphedema - Wikipedia](#)

[Maurice Klippel - Wikipedia](#)

[Paul Trénaunay - Wikipedia \(French\)](#)

[Frederick Parkes Weber - Wikipedia](#)

[Sirolimus - Wikipedia](#)

[Arteriovenous malformation - Wikipedia](#)