



3. Abnormal overgrowth of soft tissues and bones: soft tissue swelling and bone hypertrophy of the limbs are commonly observed in KTS patients, which can be progressive.
4. Lymphatic malformation: lymphatic abnormalities may also be present, often characterised by presence of superficial vascular blebs in the area of geographic stains.<sup>3</sup>

Typically, these congenital malformations affect the lower extremity unilaterally, although there are cases where malformations occur in the upper or multiple extremities.

Because KTS is characterised by the above slow-flow vascular malformations of capillaries, lymphatics and veins, the term 'capillary-lymphatico-venous malformation (CLVM) with or without overgrowth of the affected limb' is also used instead of KTS to specify patients with all of three vascular abnormalities.<sup>4</sup> Meanwhile, the term KTS is applied more broadly to include patients with only one or two vascular anomalies.

### What is the genetic basis of Klippel–Trénaunay syndrome?

KTS is one of several overgrowth syndromes, including CLOVES syndrome, which were found to be associated with *PIK3CA* mutations. These conditions, with overlapping clinical features, are also collectively known as *PIK3CA*-related overgrowth spectrum (PROS).

*PIK3CA* encodes phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha, a regulatory subunit of the enzyme phosphatidylinositol 3-kinase (PI3K). PI3K is involved in multiple signalling pathways of cell proliferation and angiogenesis, particularly the PI3K/AKT/mTOR pathway, which is important in regulating the cell cycle. Sustained activation of this pathway has been shown to cause venous malformations due to reduced apoptosis of endothelial cells and defective recruitment of vascular smooth muscles.<sup>4</sup> Activating mutations in *PIK3CA* could increase the enzyme's baseline catalytic activity, hence sustained activation of signalling pathways, which are also frequently implicated in human cancer.<sup>5</sup>

Most KTS is caused by postzygotic somatic *PIK3CA* mutations, meaning that the mutation occurs after conception, usually only found in the affected tissues. Therefore, for patients with disease aetiology of suspected somatic mosaicism, it is important to perform genetic testing in the affected tissues (for KTS it is usually the surgical specimen) rather than peripheral blood, which has very low or no yield of mutation. Correct sampling is the key to the molecular diagnosis.

For the same reason of postzygotic somatic mutation, parents often do not carry the mutation and their future reproductive risk of having another child with the same condition is low.

### What are the complications of Klippel–Trénaunay syndrome?

Major complications of KTS include the following:<sup>3,6</sup>

1. Coagulopathy and thromboembolism: KTS patients often suffer from localized intravascular coagulopathy in the areas of venous malformation, thus increased risk of superficial thrombophlebitis, deep venous thrombosis and pulmonary thromboembolism.
2. Bleeding: severity of bleeding in KTS varies from within capillary stain to severe disseminated intravascular coagulation. Intrapelvic and intra-abdominal venous malformation can result in gastrointestinal bleeding, often in the rectum.
3. Chronic venous or lymphatic insufficiency: KTS patients are at risk of chronic oedema in the affected limbs resulting from venous or lymphatic abnormalities.
4. Limb length discrepancy: length discrepancy in the lower limb could have long-term functional impact, with imbalance of the pelvis leading to secondary scoliosis and impaired gait.

5. Skin infection: KTS patients, particularly those with lymphatic abnormalities, are predisposed to recurrent cellulitis and lymphangitis, which in severe cases, could progress to bacteremia.
6. Pain: pain is a common and debilitating problem in KTS patients, which is caused by multiple factors such as chronic venous insufficiency, thrombosis and infection.<sup>7</sup>

### **What is the management of Klippel–Trénaunay syndrome?**

Management of KTS patients depends on the extent of condition and complications, which requires a multidisciplinary approach involving paediatric dermatology, orthopaedic surgery, vascular surgery and physical therapy etc. For most KTS patients, management is supportive, focusing on relieving symptoms, preventing or managing complications.<sup>1</sup> For patients with functional limbs and few or no complications, management is conservative.

Conventional treatment of the slow-flow vascular malformations in KTS include sclerotherapy and surgical resection. Recently, the use of sirolimus (also known as rapamycin), an inhibitor of mTOR, has also been shown to be effective in KTS patients refractory to conventional treatments.<sup>4,8</sup> For patients with varices or oedema of extremities, compression stocking, orthopaedic footwear, and pneumatic compression can also be used to control swelling and pain of affected limbs. Port-wine stains usually require no treatment other than laser therapy for cosmetic purpose.

Other medical or surgical interventions may be required depending on the severity of complications, for instance, medications to manage coagulopathy and pain, surgeries to manage limb-length discrepancies, embolic and haemorrhagic events.

### **References**

1. Kihiczak GG, Meine JG, Schwartz RA, Janniger CK. Klippel-Trenaunay syndrome: a multisystem disorder possibly resulting from a pathogenic gene for vascular and tissue overgrowth. *Int J Dermatol* 2006;45:883-90.
2. Oduber CE, van der Horst CM, Hennekam RC. Klippel-Trenaunay syndrome: diagnostic criteria and hypothesis on etiology. *Ann Plast Surg* 2008;60:217-23.
3. Redondo P, Aguado L, Martinez-Cuesta A. Diagnosis and management of extensive vascular malformations of the lower limb: part I. Clinical diagnosis. *J Am Acad Dermatol* 2011;65:893-906; quiz 907-8.
4. Hammer J, Seront E, Duez S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. *Orphanet J Rare Dis* 2018;13:191.
5. Luks VL, Kamitaki N, Vivero MP, et al. Lymphatic and other vascular malformative/overgrowth disorders are caused by somatic mutations in PIK3CA. *J Pediatr* 2015;166:1048-54.
6. DompMartin A, Vikkula M, Boon LM. Venous malformation: update on aetiopathogenesis, diagnosis and management. *Phlebology*. 2010; 25:224-35.
7. Lee A, Driscoll D, Glociczki P, Clay R, Shaughnessy W, Stans A. Evaluation and management of pain in patients with Klippel-Trenaunay syndrome: a review. *Pediatrics* 2005;115:744-9.
8. Adams DM, Trenor CC 3rd, Hammill AM, et al. Efficacy and Safety of Sirolimus in the Treatment of Complicated Vascular Anomalies. *Pediatrics* 2016;137:e20153257.