Klippel-Trenaunay syndrome

Klippel-Trenaunay syndrome is a condition that affects the development of blood vessels, soft tissues (such as skin and muscles), and bones. The disorder has three characteristic features: a red birthmark called a port-wine stain, abnormal overgrowth of soft tissues and bones, and vein malformations.

Most people with Klippel-Trenaunay syndrome are born with a port-wine stain. This type of birthmark is caused by swelling of small blood vessels near the surface of the skin. Port-wine stains are typically flat and can vary from pale pink to deep maroon in color. In people with Klippel-Trenaunay syndrome, the port-wine stain usually covers part of one limb. The affected area may become lighter or darker with age. Occasionally, port-wine stains develop small red blisters that break open and bleed easily.

Klippel-Trenaunay syndrome is also associated with overgrowth of bones and soft tissues beginning in infancy. Usually this abnormal growth is limited to one limb, most often one leg. However, overgrowth can also affect the arms or, rarely, the torso. The abnormal growth can cause pain, a feeling of heaviness, and reduced movement in the affected area. If the overgrowth causes one leg to be longer than the other, it can also lead to problems with walking.

Malformations of veins are the third major feature of Klippel-Trenaunay syndrome. These abnormalities include varicose veins, which are swollen and twisted veins near the surface of the skin that often cause pain. Varicose veins usually occur on the sides of the upper legs and calves. Veins deep in the limbs can also be abnormal in people with Klippel-Trenaunay syndrome. Malformations of deep veins increase the risk of a type of blood clot called a deep vein thrombosis (DVT). If a DVT travels through the bloodstream and lodges in the lungs, it can cause a life-threatening blood clot known as a pulmonary embolism (PE).

Other complications of Klippel-Trenaunay syndrome can include a type of skin infection called cellulitis, swelling caused by a buildup of fluid (lymphedema), and internal bleeding from abnormal blood vessels. Less commonly, this condition is also associated with fusion of certain fingers or toes (syndactyly) or the presence of extra digits (polydactyly).

Frequency

Klippel-Trenaunay syndrome is estimated to affect at least 1 in 100,000 people worldwide.
Genetic Changes

Klippel-Trenaunay syndrome can be caused by mutations in the PIK3CA gene. This gene provides instructions for making the p110 alpha (p110α) protein, which is one piece (subunit) of an enzyme called phosphatidylinositol 3-kinase (PI3K). PI3K plays a role in chemical signaling that is important for many cell activities, including cell growth and division (proliferation), movement (migration) of cells, and cell survival. These functions make PI3K important for the development of tissues throughout the body.

The PIK3CA gene mutations associated with Klippel-Trenaunay syndrome alter the p110α protein. The altered subunit makes PI3K abnormally active, which allows cells to grow and divide continuously. Increased cell proliferation leads to abnormal growth of the bones, soft tissues, and blood vessels.

Klippel-Trenaunay syndrome is one of several overgrowth syndromes, including megalencephaly-capillary malformation syndrome, that are caused by mutations in the PIK3CA gene. Together, these conditions are known as the PIK3CA-related overgrowth spectrum (PROS).

Because not everyone with Klippel-Trenaunay syndrome has a mutation in the PIK3CA gene, it is possible that mutations in unidentified genes may also cause this condition.

Inheritance Pattern

Klippel-Trenaunay syndrome is almost always sporadic, which means that it occurs in people with no history of the disorder in their family. Studies suggest that the condition results from gene mutations that are not inherited. These genetic changes, which are called somatic mutations, arise randomly in one cell during the early stages of development before birth. As cells continue to divide during development, cells arising from the first abnormal cell will have the mutation, and other cells will not. This mixture of cells with and without a genetic mutation is known as mosaicism.

Other Names for This Condition

- angio-osteohypertrophy syndrome
- congenital dysplastic angiopathy
- Klippel-Trenaunay disease
- KTS

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Klippel Trenaunay syndrome
Other Diagnosis and Management Resources

- Boston Children's Hospital
  http://www.childrenshospital.org/conditions-and-treatments/conditions/k/klippel-trenaunay-syndrome

- Children's Hospital of Wisconsin: Capillary Malformation (Port Wine Stain)

- Cincinnati Children's Hospital Medical Center: Capillary Lymphatic Venous Malformation
  https://www.cincinnatichildrens.org/health/c/capillary-lymphatic-venous-malformations

- Mayo Clinic: Vascular Malformation Clinic at the Gonda Vascular Center

- Seattle Children's Hospital

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html

- Drug Therapy
  https://medlineplus.gov/drugtherapy.html

- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html

- Palliative Care
  https://medlineplus.gov/palliativecare.html

- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Klippel-Trenaunay Syndrome
  https://medlineplus.gov/ency/article/000150.htm

- Encyclopedia: Port-Wine Stain
  https://medlineplus.gov/ency/article/001475.htm
• Encyclopedia: Varicose Veins
  https://medlineplus.gov/ency/article/001109.htm

• Health Topic: Vascular Diseases
  https://medlineplus.gov/vasculardiseases.html

Genetic and Rare Diseases Information Center
• Klippel-Trenaunay syndrome

Additional NIH Resources
• National Institute of Neurological Disorders and Stroke
  https://www.ninds.nih.gov/Disorders/All-Disorders/Klippel-Trenaunay-Syndrome-KTS-Information-Page

Educational Resources
• Cincinnati Children’s Hospital Medical Center: Capillary Lymphatic Venous Malformation
  https://www.cincinnatichildrens.org/health/c/capillary-lymphatic-venous-malformations

• Disease InfoSearch: Klippel Trenaunay syndrome
  http://www.diseaseinfosearch.org/Klippel-Trenaunay+syndrome/4016

• KidsHealth from the Nemours Foundation: Port-Wine Stains

• MalaCards: klippel-trenaunay-weber syndrome
  http://www.malacards.org/card/klippel_trenaunay_weber_syndrome

• Orphanet: Angioosteohypertrophic syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2346

• Seattle Children's Hospital

Patient Support and Advocacy Resources
• K-T Support Group
  https://k-t.org/

• National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/klippel-trenaunay-syndrome/

• Sturge-Weber Foundation
  http://sturge-weber.org/new-to-swf/understanding-kt.html

• Vascular Birthmarks Foundation
  https://birthmark.org/node/121
ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22Klippel-Trenaunay+syndrome%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Klippel-Trenaunay*%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D

OMIM

- KLIPPEL-TRENAUNAY-WEBER SYNDROME
  http://omim.org/entry/149000

Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/9781914

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18274338

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/9443675

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16911369

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/25681199
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4498659/

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/26268729

Reprinted from Genetics Home Reference: