KLIPPEL-TRENAUNAY & STURGE-WEBER SYNDROME

Do these 100-year-old names hold up, now that we know genetic causes?

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Vascular anomaly syndromes with eponyms such as Sturge-Weber syndrome and Klippel-Trenaunay syndrome, were described approximately 100 years ago. At that time, diagnoses were primarily based on clinical observations, as imaging studies were limited and knowledge of genetics was not as advanced as it is today. Relying solely on clinical examination made achieving an accurate diagnosis challenging then and continues to pose difficulties today.

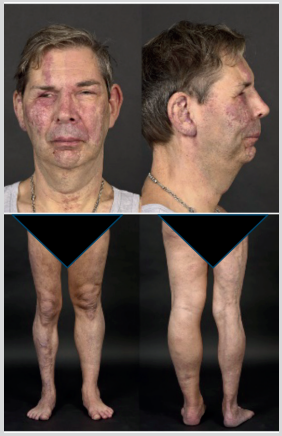
Currently, many vascular anomaly syndromes can be characterized genetically, with genetics as the most important clue to come to a diagnosis. Despite this advancement, eponyms continue to be used. Increasingly, these eponyms are associated with genetic diagnoses, offering a new perspective on the naming and genetic classification of disorders. This evolution brings the possibility of targeted therapeutic options, suggesting that completely 'saying goodbye' to well-known and frequently used eponyms might not be desirable yet.

Conditions such as Sturge-Weber Syndrome (SWS) and Klippel-Trenaunay Syndrome (KTS) are regularly discussed in the doctor's office, with the important question: do I have it, do I have both (or do I have neither)? More specifically, in the case of extensive port-wine stains on the face, do I have SWS? And in the case of extensive port-wine stains on a leg or arm, do I have KTS? And what if I have both a port-wine stain on the face and on one or more limbs, or even more extensive port-wine stains, do I have two (rare) disorders or just one? and which one? In general, it should be noted that the chance of a patient having two rare disorders is very exceptional.

Case

Before we try to answer this question, let me introduce you to a patient, a 57-year-old man (Figure 1). In summary, he has extensive port-wine stains on the face, glaucoma, aura migraine, but no epilepsy. In addition, there is extensive port-wine staining of the right leg, which is also shorter and thinner and has varicose veins.[1] This man's question was also: do I have SWS and KTS? This question will be answered at the end of this article.

Vascular anomalies in the newborn



Source: Radboud University Medical Centre

Figure 1: Clinical images of the patient.

Let's begin at the very start: with a newborn. It's well-known that many (vascular) birthmarks are not visible on the (20 weeks) ultrasound, but become apparent at birth. There is often a lot of uncertainty in the beginning after the understandable initial shock of the parents and care providers. Questions arise: Is it a stork bite, which will go away by itself? Or is it a (precursor to) an infantile haemangioma that also often improves spontaneously? Or is it a port wine stain?[2] With port-wine stains, there are many questions about laser treatment in the beginning: how do we get rid of the stain? Or is there more to it than just the visible spot, or is it an indicator of underlying problems? A syndrome such as SWS or KTS?[3] And if the patient's parents start searching the internet with this keyword, it can provide answers but also cause a lot of anxiety.

History of Sturge-Weber syndrome

Let us go back to the basics and the history of SWS. In 1860, Dr. R. Schirmer described the combination of angioma (port-wine stain) of the face and larger eye (buphthalmos; glaucoma).[4] Later, in 1879, Dr. W.A. Sturge identified a patient with the combination of a port-wine stain on one side of the

face with neurological problems on the other side of the body (contralateral).[5] In 1922, Dr. F. Parkes Weber described a patient showing radiological abnormalities with calcifications on one side of the brain, alongside a port-wine stain and glaucoma on the same side, but with paralysis on the other side of the body.[6]

In 1935, K.J. Hilding Bergstrand coined the term 'Sturge-Weber Syndrome' in recognition of Dr. Sturge and Dr. Weber.[7] It is important to remember that around the year 1900, there were no options for ultrasound, MRI or genetic analysis available.

Clinical characteristics of Sturge-Weber syndrome *

SWS as we know it today classically includes a port-wine stain of the forehead, situated at the innervation area of the 1st (upper) branch of the 5th cranial nerve (V1; nervus V; trigeminal nerve), which is responsible for the sensation of the face. (Figure 2) In addition, there is glaucoma with vascular abnormalities of the eye and angiomatosis of the meninges in the parieto-occipital region, with calcifications and the risk of epilepsy on the ipsilateral side (same side) of the port-wine stain, and risk of paralysis contralaterally (opposite side). The combination of a port-wine stain on the forehead, glaucoma and epilepsy is the classic triad of SWS.

SWS is estimated to occur in 1 out of every 20,000 to 50,000 births, with no difference between boys and girls. While ordinary port-wine stains without additional problems occur more often: 3:1000 children, the risk of SWS in babies with a facial port-wine stain is ± 8%. The risk increases to ±78% If the skin area of V1 is completely affected and ±26% if partially affected. The likelihood further increases if the forehead is affected bilaterally and if there is involvement of the upper eyelid or extension of V1 to the rest of the face (V1 ± V2 and V3; Figure 2).

If there is a predisposition to epilepsy, it almost always manifests itself before the age of 2, but sometimes in adulthood. In 30% of the patients, epilepsy starts during a fever; this susceptibility to seizures during a fever remains.

Screening for SWS in babies with facial port-wine stains can be done with brain MRI with contrast, but the optimal age for screening is not clear. Generally, SWS is unlikely in normally developing children with a normal MRI and a normal neurological examination after the age of 1 year. An MRI with contrast is not sensitive in newborns.[7]

History of Klippel-Trenaunay syndrome

Klippel-Trenaunay Syndrome[9] was first described in 1900 by the French neurologist, Dr. Maurice Klippel and the Parisian physician, Dr. Paul Trenaunay. They described it as a congenital, sporadic (non-hereditary) disorder characterized typically by a triad (usually in a limb or quadrant) of symptoms

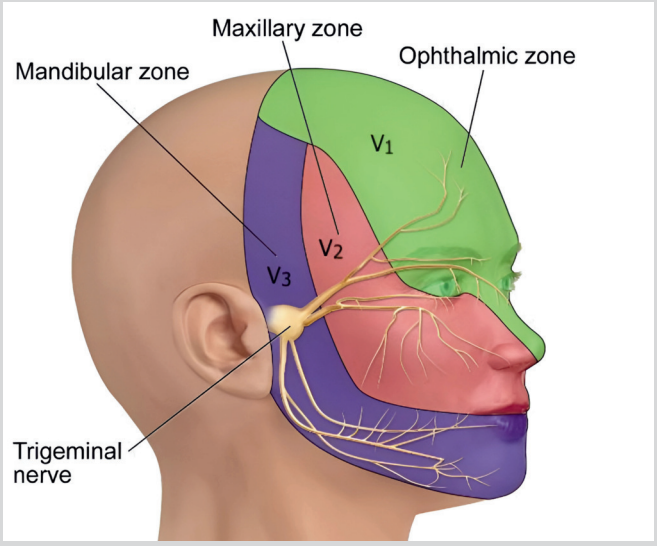


Figure 2: Branches of the 5th cranial nerve (nervus V; trigeminal nerve) responsible for the sensation of the face[8]

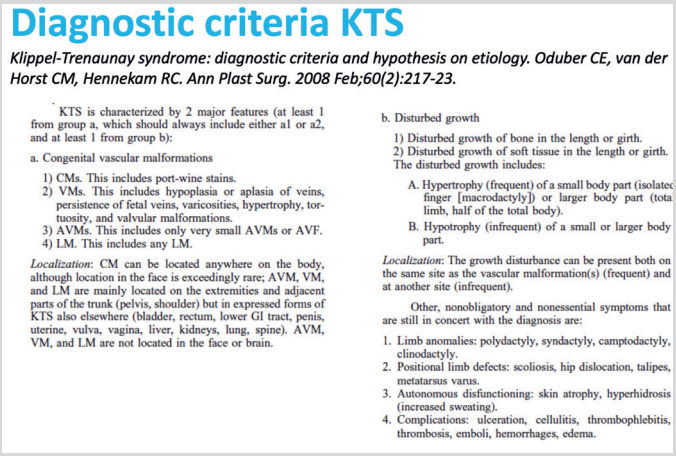
Source: https://www.sturgewebersyndrome.life

1. Port-wine stain *'haemangioma'* of the skin
2. Varicose veins in abnormal places, especially on the lateral side of the leg and or venous of lymphatic vascular malformations
3. Bone and soft tissue limb overgrowth.

As mentioned earlier, around 1900 there were no options for ultrasound, MRI or genetic analysis. This makes descriptions from that era particularly clinical and also makes the question of 'what exactly is KTS and what is not' difficult to answer, even in the present day. This is because sometimes the classical triad is not always complete, and one of the symptoms may be missing. Sometimes, there is undergrowth instead of overgrowth, or there are anomalies outside the quadrant, formerly also referred to as Proteus syndrome. In the past, this clinical picture was referred to as a 'forme fruste' of KTS, an atypical or weakened manifestation.[10,11]

Much has been written in recent years about what exactly KTS is or is not, and what criteria should be applied now that we have ultrasound and MRI. However, as of 2008, precise diagnosis still proved to be a difficult task. At that time, there was insufficient knowledge of genetics. The diagnostic criteria for KTS were then described in the article by Oduber et al.[12] as shown in Figure 3. What is striking is that they needed a lot of words to describe the precise criteria for KTS.

* **Editorial Note:** For more information Sturge Weber Syndrome and the treatment of port-wine stains by laser, see the article "Port Wine Stains/ Capillary Malformation and Sturge-Weber Syndrome: Frequently Asked Questions Regarding Laser Treatment" by Dr. Eulalia Baselga on pages 40-42 of VASCA Magazine #2. Available here: https://vascern.eu/app/uploads/2024/05/VASCA-Magazine-Edition-2.pdf



Diagnostic criteria KTS

Klippel-Trenaunay syndrome: diagnostic criteria and hypothesis on etiology. Oduber CE, van der Horst CM, Hennekam RC. Ann Plast Surg. 2008 Feb;60(2):217-23.

KTS is characterized by 2 major features (at least 1 from group a, which should always include either a1 or a2, and at least 1 from group b):

a. Congenital vascular malformations

1) CMs. This includes port-wine stains.
2) VMs. This includes hypoplasia or aplasia of veins, persistence of fetal veins, varicosities, hypertrophy, tortuosity, and valvular malformations.
3) AVMs. This includes only very small AVMs or AVF.
4) LM. This includes any LM.

Localization: CM can be located anywhere on the body, although location in the face is exceedingly rare; AVM, VM, and LM are mainly located on the extremities and adjacent parts of the trunk (pelvis, shoulder) but in expressed forms of KTS also elsewhere (bladder, rectum, lower GI tract, penis, uterine, vulva, vagina, liver, kidneys, lung, spine). AVM, VM, and LM are not located in the face or brain.

b. Disturbed growth

1) Disturbed growth of bone in the length or girth.
2) Disturbed growth of soft tissue in the length or girth. The disturbed growth includes:

A. Hypertrophy (frequent) of a small body part (isolatec finger [macrodactyly]) or larger body part (tota limb, half of the total body).

B. Hypotrophy (infrequent) of a small or larger body part.

Localization: The growth disturbance can be present both on the same site as the vascular malformation(s) (frequent) and at another site (infrequent).

Other, nonobligatory and nonessential symptoms that are still in concert with the diagnosis are:

1. Limb anomalies: polydactyly, syndactyly, camptodactyly, clinodactyly.
2. Positional limb defects: scoliosis, hip dislocation, talipes, metatarsus varus.
3. Autonomous disfunctioning: skin atrophy, hyperhidrosis (increased sweating).
4. Complications: ulceration, cellulitis, thrombophlebitis, thrombosis, emboli, hemorrhages, edema.

Figure 3: Diagnostic criteria KTS as described in 2008[12]

Source: Oduber CNEU et al., 'Klippel-Trenaunay Syndrome - Diagnostic Criteria and Hypothesis on Etiology,' Ann Plas Surg, Feb 2008

Differential diagnosis of Klippel-Trenaunay syndrome

If it is not KTS, what could it be? This differential diagnosis of KTS is detailed in Table 1.[13-16] Making the correct diagnosis is still a challenge.

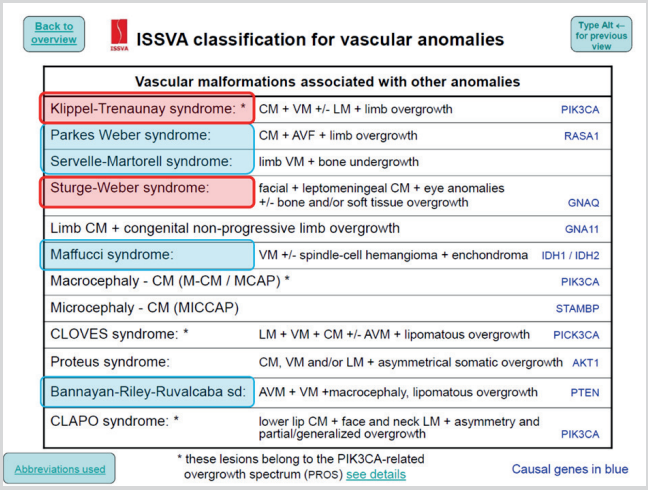
	Acronym	Characteristics	DNA
Large port-wine stain		No additional problems	GNAQ - GNA11 - PIK3CA - KRAS - NRAS
DCMO	Diffuse capillary malformation with overgrowth		? - PIK3CA
Proteus syndrome		Progressive overgrowth of the bones, skin, and other tissues	AKT1
Parkes Weber syndrome		Overgrowth in combination with capillary malformations and arteriovenous fistulas	RASA1 - EBHP4
CMTC	Cutis marmorata telangiectasia congenita		? – GNA11
CLOVES	Congenital Lipomatous Overgrowth, Vascular anomalies, Epidermal nevi, and Skeletal deformities/ Scoliosis.		PIK3CA
FAVA	Fibro-Adipose Vascular Anomaly		PIK3CA
M-CM/ MCAP	Megalencephaly-capillary malformation syndrome		PIK3CA

Table 1: Differential diagnosis of KTS[13-16].

Source: Clemens RK et al., Vasa, Mar 2015; Uller W et al., Semin Pediatr Surg, Aug 2014; Lee MS et al., J Am Acad Dermatol, Oct 2013; Schuart C et al., Eur J Med Genet, May 2022.

Eponyms

Before we go any further, we need to understand eponyms. An eponym is a new word, based on the name of a person or place. Examples of eponyms are Sandwich: named after the Earl of Sandwich or Fahrenheit: named after Gabriel Fahrenheit, and of course Champagne: the drink named after the region where it is produced.



Back to overview

ISSVA classification for vascular anomalies

Type Alt ← for previous view

Vascular malformations associated with other anomalies		
Klippel-Trenaunay syndrome: *	CM + VM +/- LM + limb overgrowth	PIK3CA
Parkes Weber syndrome:	CM + AVF + limb overgrowth	RASA1
Servelle-Martorell syndrome:	limb VM + bone undergrowth	
Sturge-Weber syndrome:	facial + leptomeningeal CM + eye anomalies +/- bone and/or soft tissue overgrowth	GNAQ
Limb CM + congenital non-progressive limb overgrowth		GNA11
Maffucci syndrome:	VM +/- spindle-cell hemangioma + enchondroma	IDH1 / IDH2
Macrocephaly - CM (M-CM / MCAP) *		PIK3CA
Microcephaly - CM (MICCAP)		STAMBP
CLOVES syndrome: *	LM + VM + CM +/- AVM + lipomatous overgrowth	PICK3CA
Proteus syndrome:	CM, VM and/or LM + asymmetrical somatic overgrowth	AKT1
Bannayan-Riley-Ruvalcaba sd:	AVM + VM +macrocephaly, lipomatous overgrowth	PTEN
CLAPO syndrome: *	lower lip CM + face and neck LM + asymmetry and partial/generalized overgrowth	PIK3CA

Abbreviations used

* these lesions belong to the PIK3CA-related overgrowth spectrum (PROS) see details

Causal genes in blue

Figure 4: Screenshot of ISSVA classification with different eponyms[17]

Source: ISSVA Classification; https://www.issva.org/classification

Within the worldwide ISSVA classification[17] for vascular anomalies, eponyms such as KTS, SWS, Parkes-Weber syndrome, etc. are still used. (Figure 4). The use of eponyms such as Klippel-Trenaunay Syndrome has several benefits; it provides clarity for the patient and describes a clinical risk profile such as the increased risk of thrombosis. However, eponyms also have drawbacks. For example, they never describe the severity of the condition in an individual patient and do not reflect the spectrum of a condition. In daily practice, it appears that the diagnosis of KTS is regularly made or considered, which causes a lot of anxiety.

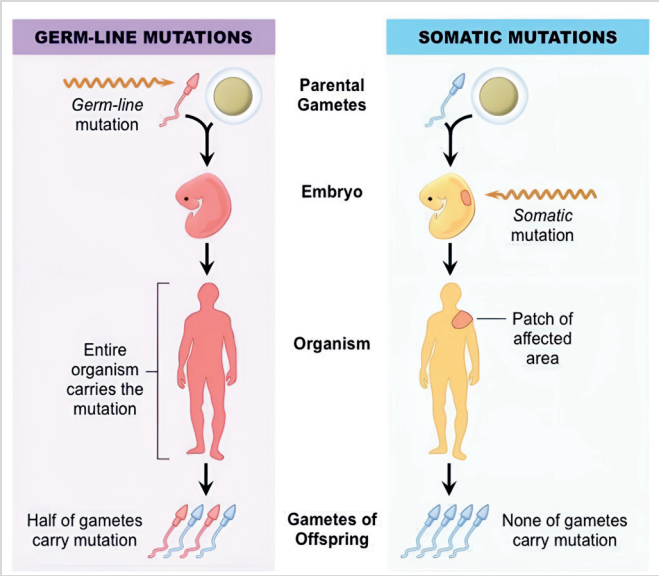


Figure 5: Schematic representation of Germ-line Mutations (left panel) versus Somatic Mutations (mosaicism; right panel)[21].

Source: https://ib.bioninja.com.au/standard-level/topic-3-genetics/33-meiosis/somatic-vs-germline-mutatio.html

Genetics of vascular anomalies

Today, knowledge of genetics does provide more insight into the causes of these vascular anomalies such as SWS[18] and KTS[19]. This has made accurate diagnosis easier. We know that many vascular anomalies are caused by DNA mosaicism (somatic mutation), located only in the affected tissues and not in all cells of the organism, where the DNA abnormalities activate the tissue and increase cell division and tissue and blood vessel growth (Figure 5)[20]. This explains why the disorders are not hereditary and occur sporadically.

As of 2011, many genes are known to be associated with vascular anomalies (Figure 6). In 2013, SWS was found to be associated with a GNAQ mutation,[18] but 'ordinary' port-wine stains were also found to have the same GNAQ mutation as SWS patients. The 2013 article wrote: "This finding confirms a long-standing hypothesis."

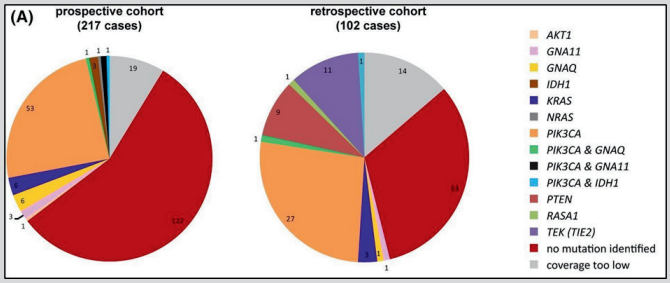


Figure 6: Genes found in tissue of vascular anomalies-patients in two large cohorts from one vascular anomalies center[22]

Source: Ten Broek RW et al., 'Comprehensive Analysis of Vascular Malformations,' Genes Chromosomes Cancer, Aug 2019.

How (and when) does SWS occur? SWS occurs in the 1st trimester of pregnancy (weeks 5-8), when the skin (of the forehead) and the primitive brain and eye are close to each other. A somatic mutation involving these embryological tissues appears to be the cause for the occurrence of SWS. The timing (and cell type) of the GNAQ mutation during embryonic development likely has implications for whether one has only facial port-wine stains, or also eye or brain abnormalities, where one can imagine that the earlier in the embryonic phase the mutation occurs, the more extensive the consequences will be. Some of the clinical variability may also be explained by mutations different from the mutation in the GNAQ gene, as we will find out at the end of this article.

In 2016, KTS was reported to be associated with a PIK3CA mutation.[19] This mutation also occurs early in pregnancy (weeks 5-8). The PIK3CA mutation causes the affected cells to become more active, which explains the overgrowth and increased vessel growth. It now appears that there are several conditions that have the same PIK3CA mutation, with the difference here too being caused by a difference in timing, location and cell type of the mutation.

All conditions with PIK3CA mosaicismé[23] are now categorised as:

- PIK3CA Related Overgrowth Spectrum (PROS) like e.g., CLOVES syndrome, FAVA, Facial Infiltrating Lipomatosis (FIL) or KTS. **
- PIK3CA related vascular malformations like e.g., common venous or lymphatic malformations.
- PIK3CA related non-vascular abnormalities like e.g., epidermal nevi or seborrheic keratoses.

While we used to try to distinguish the different diseases, it now appears that they are caused by the same mutation/mechanism, which is also evidenced by the overlap of clinical features seen in typical PROS patients. For example, people can have the characteristics of KTS but also of FIL combined with an epidermal nevus[24].

All these developments provide a new perspective on the naming of disorders. This raises the question, can you have KTS without PIK3CA? The consensus is that this is not the case. However, there are other syndromes that resemble KTS with an asymmetry of the legs, large (extensive) port-wine stains and varicose veins, but do not have all the features or have other features, for example, undergrowth instead of overgrowth. It now appears that these are expressions of a mutation other than the PIK3CA mutation, for example of the GNAQ gene, the GNA11 gene or other genes, such as KRAS. And then we see the condition may look like KTS, but it (really) is not[25].

Return to the case

Returning to the case of the 57-year-old man with port-wine stains on his face and leg.[1] Tissue biopsies were taken from the skin of his face and leg, and genetic investigations showed the same mutation in both tissues: GNA11.

The GNA11 gene belongs to the 'family of' GNAQ genes; genes that both code for G-proteins. Based on this, it is understandable that a GNA11 mutation gives a SWS-like picture. The patient's question of whether he has SWS and KTS has now been answered: actually, he has neither. Or you could call his condition: GNA11-SWS.

This case highlights the growing recognition of patients with GNA11 mosaicism, many of whom also have a clinical picture similar to SWS, but generally milder. Notably, if there are neurological problems such as epilepsy, they do not develop until later in life[1].

Goodbye to eponyms?

Can we now say goodbye to eponyms like SWS and KTS? Because of the overlapping combinations of symptoms, the use of eponyms (as described in ±1900) is becoming less useful, while classification according to the causative muta-

**** Editorial Note:** For more information on PROS syndrome, see the article "*PROS Syndrome*" by D. Maroeska W.M. te Loo on pages 26-27 of VASCA Magazine #1. Available here: https://vascern.eu/app/uploads/2023/06/VASCA-Magazine-Edition-1.pdf

tion is becoming more useful. However, it may be too early to do away with them altogether.

In current medical practice, terminology options could include:

- Large port-wine stain; does not look like a syndrome
- Port-wine stain
  - o In clinical spectrum SWS/KTS
  - o Possibly GNAQ/GNA11
  - o Possibly PIK3CA
  - o Does not appear to be PIK3CA related
  - o No mutation found yet
- Or, for example, mention both clinical and genetic diagnosis such as GNAQ-SWS or GNA11-SWS, as mentioned above in the case of our patient.

The 'forms frustes' or the conditions in which no genetic abnormality has (yet) been found, may be the result of another genetic cause that is not yet known; we will have to keep describing this group clinically but this is all still in its infancy.

Wrapping up

For all disorders, and of course also for vascular anomalies, classification (and making the correct diagnosis) is essential. Today, we are moving from a clinical to a genetic classification. Genetic screening provides more insight into the exact classification and thus clarity for (the parents of) the patient. Moreover, genetic classification will also lead to a rational target for therapy (targeted therapy)[20,23,26,27] offering new perspectives. But again, medical science is still searching. Much is already known about sirolimus (rapamycin) inhibiting the PI3K/AKT/mTOR pathway via mTOR inhibition (Figure 7). Other, and more specific inhibitors are still in the research phase, hopefully offering more in the future for people with difficult-to-treat conditions.

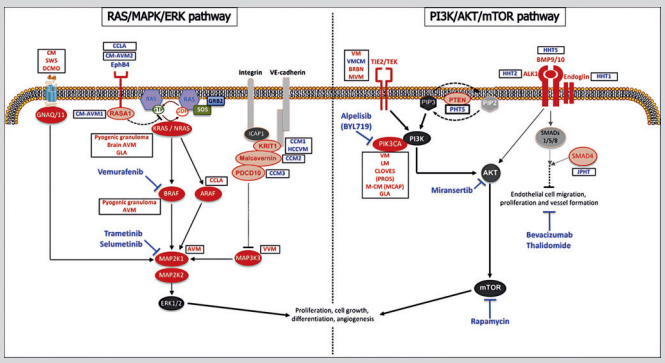


Figure 7: Theranostics in vascular anomalies; the RAS/MAPK/ERK and PI3K/AKT/mTOR pathways hyperactivated in vascular malformations. Targeted treatments noted in blue[27].

Source: Dekeuleneer V et al., 'Theranostic Advances in Vascular Malformations,' J Invest Dermatol, Apr 2020..

Genetics and theranostics (a combination of diagnostics and therapy) offer a new and hopeful perspective in the treatment of the syndromes in the clinical spectrum of SWS and KTS, terms that are still recognised and therefore remain usable in practice. So, we will not say goodbye to the eponyms yet, but in the future, clinical diagnosis will increasingly be combined with genetic diagnosis, as in our patient with GNA11-SWS.

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This is the first article in the new era of VASCA magazine, which is moving to online articles. We are pleased to share it here to ensure that its valuable insights reach our community.

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