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Genetics Update for Pediatricians: New Therapies and Old diagnoses in 2021



Disclosure Statement

» **Dr. Robin D. Clark is an author of Genetic Consultations in the Newborn, a book published by Oxford University Press.**



Learning Objectives

- » Anticipate common sequelae in these genetic disorders:
 - ~ **Down syndrome:** transient abnormal myelopoiesis
 - ~ **Klinefelter syndrome:** neurodevelopmental issues
 - ~ **Achondroplasia:** apparent life-threatening events
 - ~ **Tuberous sclerosis:** seizures & neurocognitive issues
 - ~ **Klippel-Trenaunay syndrome:** tissue overgrowth
- » Be familiar with therapy that prevents or ameliorates common complications associated with these disorders.



Down syndrome (DS) and Transient Abnormal Myelopoeisis (TAM)

- » TAM is also known as **transient leukemia, transient myeloproliferative disorder, transient leukemoid reaction**
- » Occurs in ~**10%** of infants with DS.
- » TAM was considered to be benign, “self-limiting” with a favorable prognosis, except for a risk for later development of acute myeloid leukemia.
 - ~ Most newborns with TAM are **asymptomatic** and only present with circulating blast cells, with or without leukocytosis.
 - ~ In 66-84%, TAM **spontaneously resolves**: blasts and symptoms regress by 3 months without intervention.
 - ~ TAM may be “**silent**”: asymptomatic patients with DS may have a small abnormal clone that is not clinically apparent



TAM is Symptomatic in 15-30%

» Liver disease

- ~ **Hepatosplenomegaly**
- ~ Abnormal liver transaminases and coagulation tests 25%
- ~ **Jaundice** 25%
- ~ **Coagulopathy**
- ~ **Liver fibrosis** due to blast cell infiltration that can rarely cause fulminant liver failure, in up to 10%,

» Skin rash

» Anemia

- ~ **Hydrops fetalis**, ascites, pericardial/pleural effusion
- ~ **Thrombocytopenia, leukocytosis**

» Early death in approx. 10%

» Progression to **ML-DS** in approx. 20%

Watanabe K. Recent advances in the understanding of transient abnormal myelopoiesis in Down syndrome. *Pediatr Int.* 2019 Mar;61(3):222-229.. PMID: 30593694



TAM can progress to Acute Myeloid Leukemia (ML-DS)

- » Children with Down syndrome have a 10-20 fold increased risk of developing **acute leukemia**.
 - ~ Acute megakaryoblastic leukemia (AMKL or **Acute myeloid leukemia associated with Down syndrome, ML-DS**) is **500 times higher** in children with DS than in children without DS
 - ~ Most cases occur within the **first 4 years of life**; median age 1.8 years.
- » Antecedent **preleukemic TAM occurs in 20–30% of ML-DS**
- » Chemotherapy with **cytarabine**
 - ~ ML-DS cells have a 12-fold **increase in sensitivity** to cytarabine compared with non-DS AML cells

Kudo K. Myeloid Leukemia Associated with Down Syndrome. March 6th 2013. DOI: 10.5772/52784



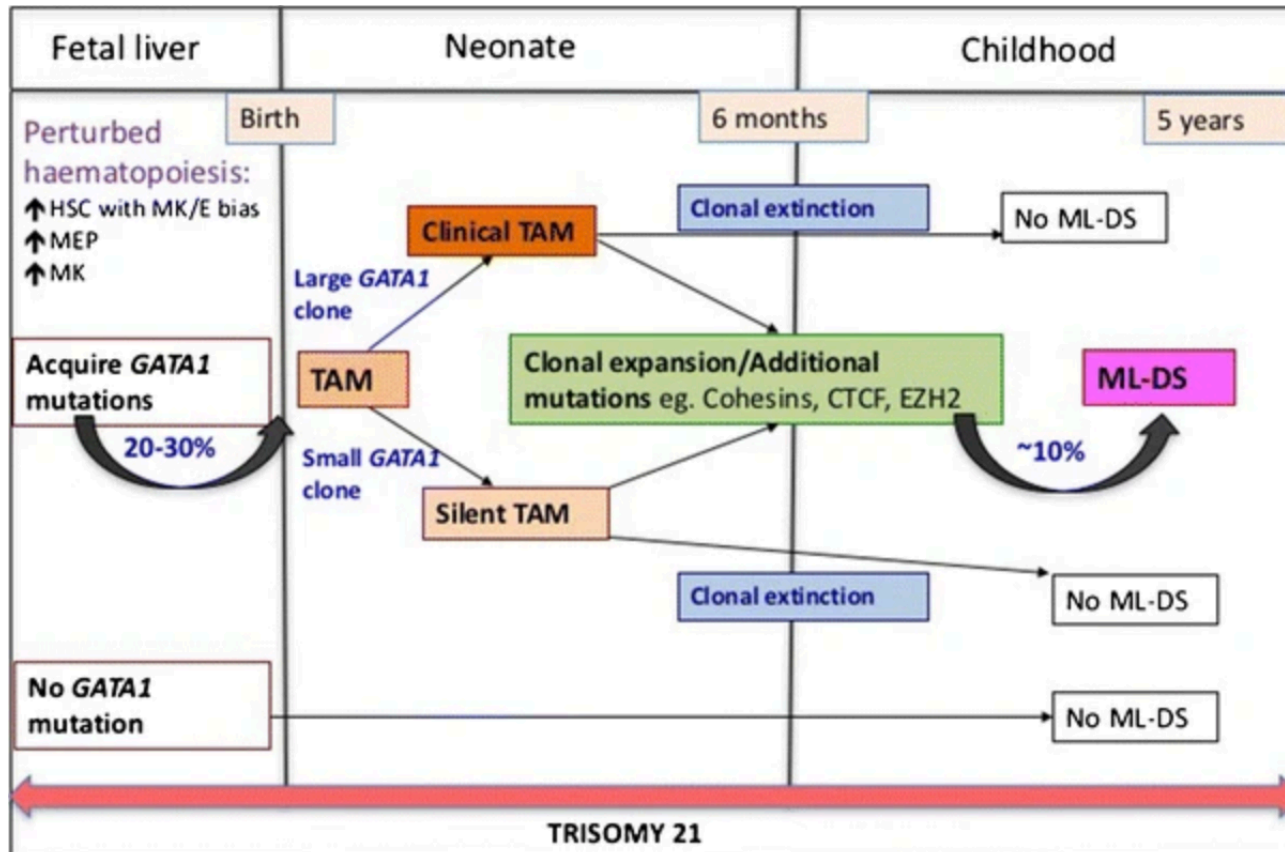
TAM can cause Early Death

- » In 2006, Children's Oncology Group (COG) reported a prospective study
- » Natural history of **48** children with DS and TAM.
- » **Leukemia** occurred in **19%** of infants at a mean age 20 months
- » **Early death** occurred in **17%** of infants
- » Death was significantly correlated with
 - ~ **higher WBC** count at diagnosis
 - ~ **increased bilirubin and liver enzymes**
 - ~ **failure to normalize the blood count**

Massey GV, *et al*: A prospective study of the natural history of transient leukemia (TL) in neonates with Down syndrome (DS): Children's Oncology Group (COG) study POG-9481. *Blood* 107(12): 4606-13, 2006:57-65



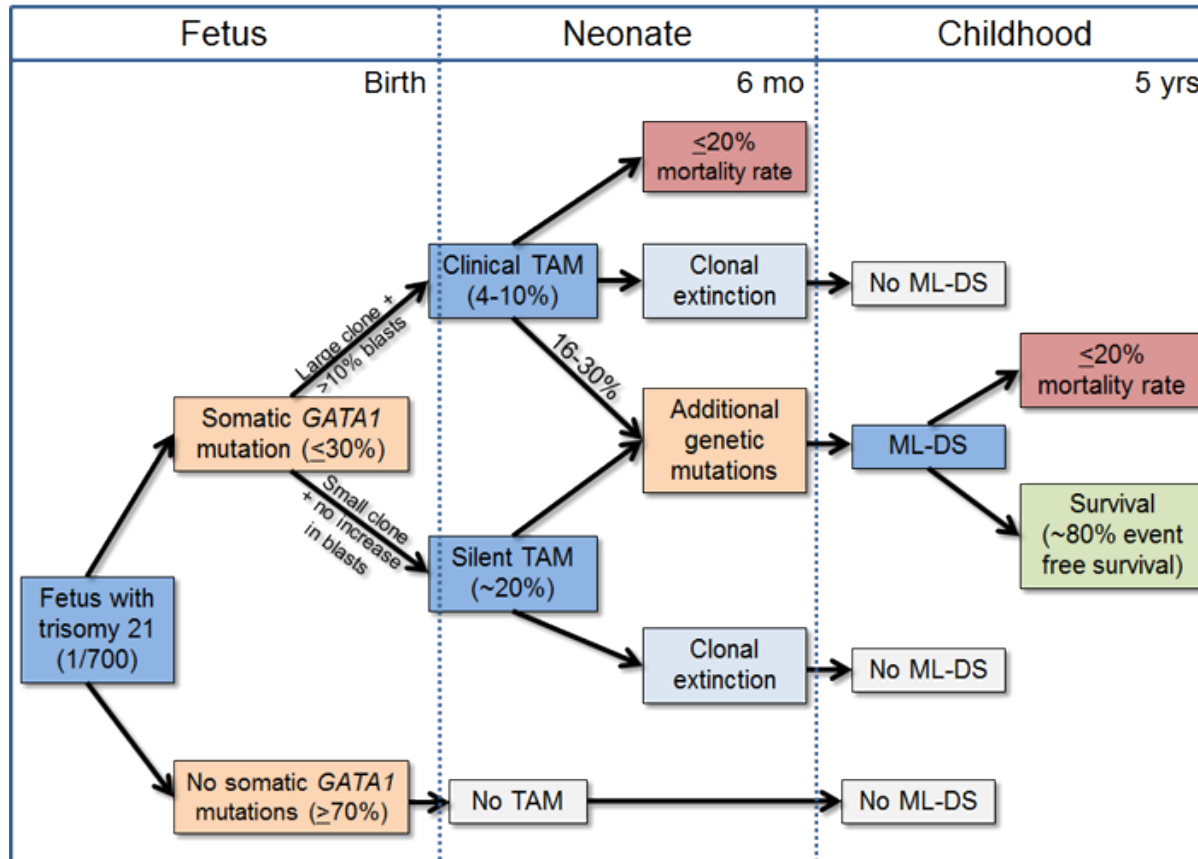
TAM is of fetal onset: Occurs in 20-30% of DS with an acquired clonal *GATA1* variant



Bhatnagar N, *et al.* (2016). Transient Abnormal Myelopoiesis and AML in Down Syndrome: an Update. *Current Hematologic Malignancy Reports*, 11, 333 - 341. PMID [27510823](https://pubmed.ncbi.nlm.nih.gov/27510823/)



Additional genetic variants transform TAM to ML-DS

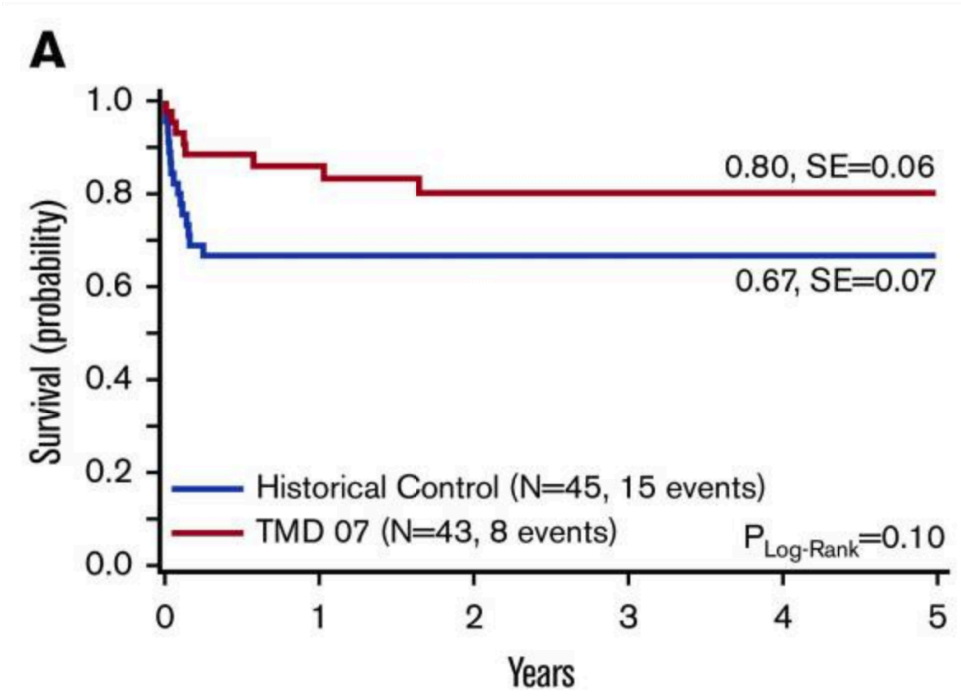


Adapted from Bhatnagar *et al.*, 2016 and Mateos *et al.*, 2015. PMID [26835364](https://pubmed.ncbi.nlm.nih.gov/26835364/)



Low dose cytarabine reduces mortality in TAM

- » Chemotherapy with **low dose cytarabine** (LDCA, cytosine arabinose) **reduces mortality** in infants with severe life-threatening symptoms of TAM.
- » The TMD Prevention 2007 trial showed **improved survival** among 43 infants treated with LDCA.
- » Treatment **did not prevent disease progression** to ML-DS



Flasinski M, *et al.* Low-dose cytarabine to prevent myeloid leukemia in children with Down syndrome: TMD Prevention 2007 study. *Blood Adv.* 2018 Jul 10;2(13):1532-1540. PMID: 29959152



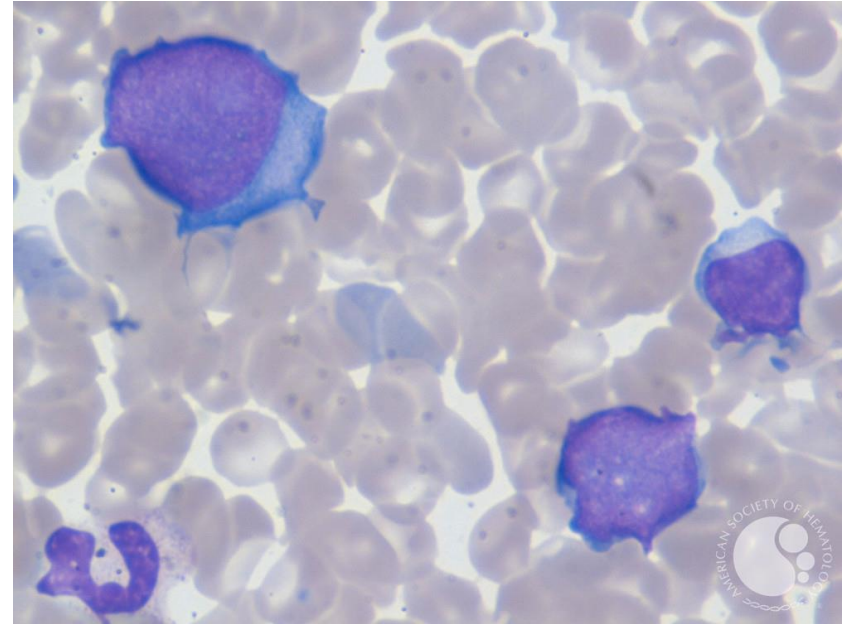
Important points: Down syndrome & TAM

» Points to know:

- ~ TAM is **not always benign**. It can lead to ML-DS or death.
- ~ **Low dose cytarabine decreases mortality** in severe TAM
- ~ **GATA1 variant analysis** identifies both clinical and silent TAM
 - It is not currently the standard of care to check for GATA1 clonal variants in all patients with Down syndrome.

» Things to do:

- ~ Order **peripheral blood smear with differential** in all infants with DS
 - At birth and q 3 mos until 4 yrs when risk of leukemia is reduced
- ~ Refer babies with TAM to Genetics and Heme-Onc

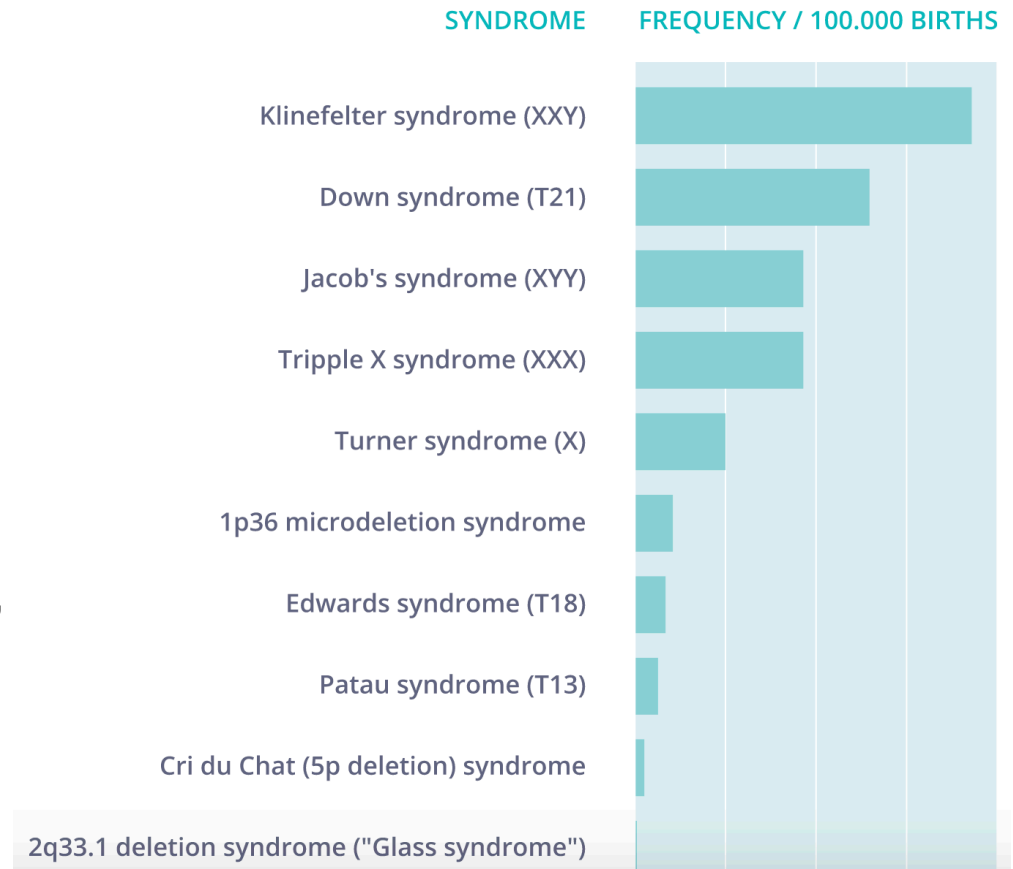


- » Blasts (large homogeneous nuclei, cytoplasmic blebs) are apparent in this image but may not be evident in silent TAM



Klinefelter syndrome, 47,XXY, is common

- 47,XXY is the **most frequent** chromosome disorder in men
 - 1-2 live-born boys/1000 births
 - **For every 2 boys with Down syndrome, there are 3 boys with KS.**
- Diagnose with a **karyotype**
 - 80%-90% 47,XXY
 - 10%-20% mosaicism: 46,XY/47,XXY, isochromosome X, or a higher number of X chromosomes
- Consider adding **microarray** in infants with KS and co-morbidities



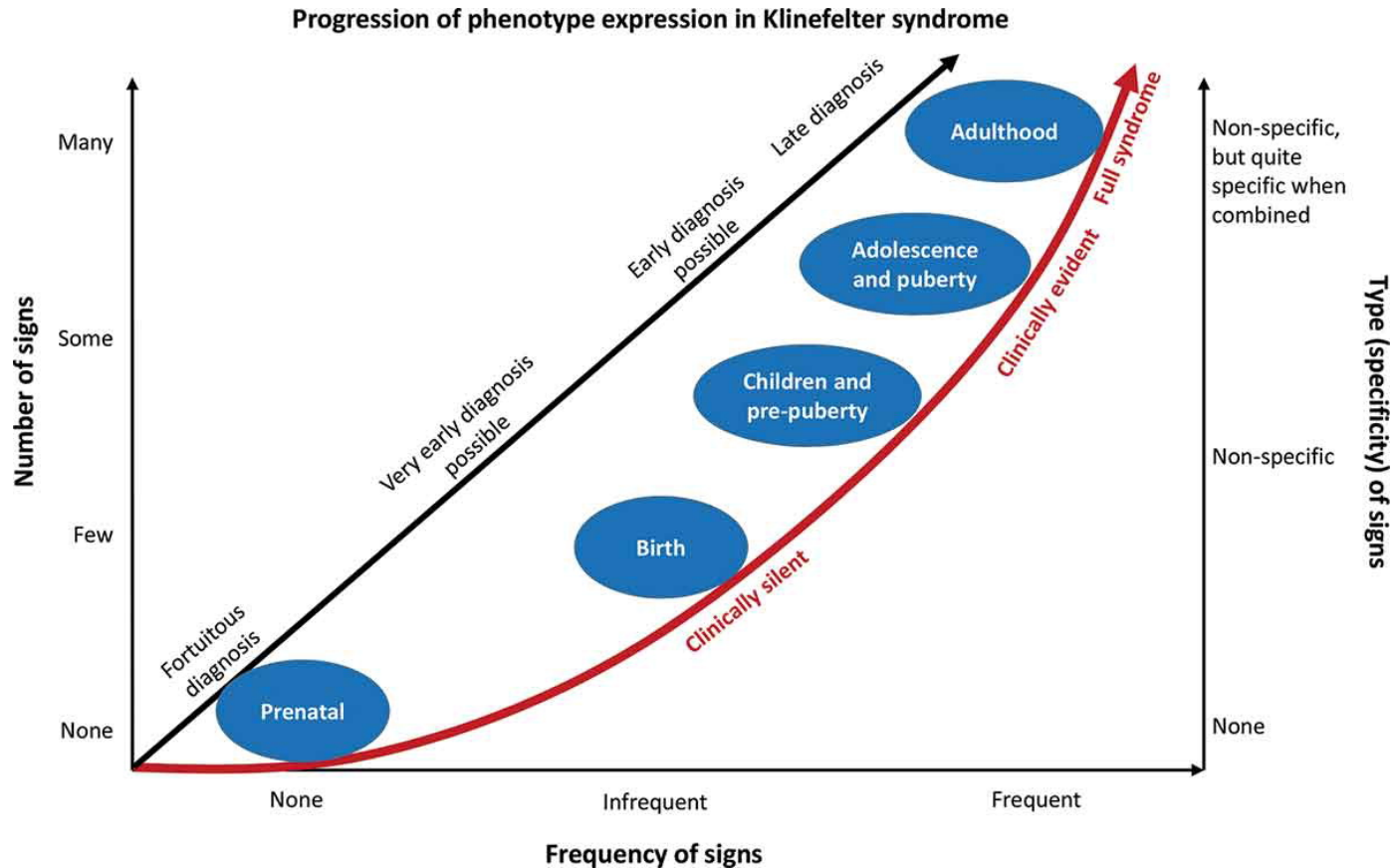
47,XXY, is variable and often undiagnosed

- » Largely **undiagnosed or diagnosed later** in adulthood.
 - ~ Only 25% to 40% of subjects with 47,XXY KS are **ever** diagnosed
 - ~ Prenatal dx 15–20%, before puberty 10%, puberty 15%, adult 50–60%, usu. during fertility workup.
- » Phenotype is **variable and usually mild**
 - ~ **Androgen deficiency** affects **endocrine, central nervous system and neurodevelopmental function**.
 - Classic: hypogonadism, small or undescended testes, small phallus or micropenis, eunuchoid, gynecomastia, elevated gonadotropins, azospermia
 - Increased height, clinodactyly fifth finger, pes planus, osteoporosis, truncal obesity, leg ulcers.
 - ~ Neurologic features
 - Truncal **hypotonia** >80%, delayed motor planning skills, positional torticollis ~30%
 - “Quiet baby” phenotype: orofacial hypotonia, speech delays, and androgen deficiency
 - ~ Neurocognitive and psychosocial manifestations
 - Increased risk for **anxiety** but decreased risk for autistic traits
 - **Delayed speech**, expressive > receptive, **dyslexia, dysgraphia**
 - Intact neurocognitive function: **verbal IQ < performance IQ** but remains within normal limits.
 - ~ 48,XXXYY and 49,XXXXYY and/or additional chromosome microdeletions or duplications: more severe phenotype, distinct clinical features, and higher diagnostic rate

Samango-Sprouse C, *et al.* Klinefelter Syndrome and Turner Syndrome. *Pediatr Rev.* 2021 May;42(5):272-274.
doi: 10.1542/pir.2020-004028. PMID: 33931514



Klinefelter syndrome, 47,XXY, is usually diagnosed in adulthood



Alberto Ferlin (2020) Strategies to improve early diagnosis of Klinefelter syndrome, Expert Review of Endocrinology & Metabolism, 15:6, 375-378, DOI: [10.1080/17446651.2020.1831912](https://doi.org/10.1080/17446651.2020.1831912)



Early detection of Klinefelter syndrome, 47,XXY, is possible with NIPT (non-invasive prenatal test)

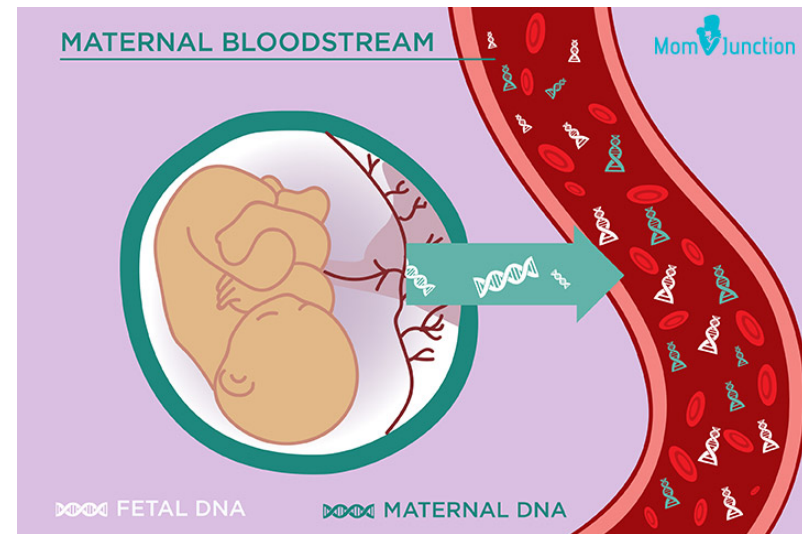
Table 4

PPV of NIPT in different SCA disease.

	NIPT+	TP	FP	No diagnosis	PPV %
Tumer syndrome	27	5	12	10	29.41 (5/17)
Klinefelter syndrome	12	7*	2	3	77.78 (7/9)
XXX syndrome	8	5	0	3	100 (5/5)
XYY syndrome	3	1	0	2	100 (1/1)
ChrX-(Y)	7	0	1	6	—
Total	57	18	15	24	54.54

FP=false positive, NIPT = noninvasive prenatal testing, NIPT+=NIPT positive result, PPV = positive predictive value, SCA = sex chromosomal aneuploidies, TP=true positive.

*Two cases were detected chromosome X partial duplication (0.4 and 0.8 Mb) by Chromosomal Microarray Analysis in amniotic fluid cells, while not clear cause disease.



Yu B, *et al.* Overall evaluation of the clinical value of prenatal screening for fetal free DNA in maternal blood. *Medicine*.

2017;96:27(e7114)



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Boys with KS benefit from early dx and treatment

- » **Advantages of early diagnosis:** Lifestyle management, timely speech and learning support, timely testosterone treatment and fertility preservation
 - ~ **Physical therapy** prevents plagiocephaly, minimizes gross motor delays.
 - ~ **Endocrine therapy is not just for puberty**
 - **In older boys** with low levels of testosterone: improve **muscle mass, bone strength** and pubertal development.
 - ~ Rate of **osteoporosis** and **fractures** in adult men with KS correlates to age at dx
 - **Early hormonal treatment**, although not yet standard of care, improve **neurodevelopment** in infants.
 - ~ 3 monthly injections of 25 mg of testosterone enanthate at 4-12 months.
 - This **mimics the normal male “mini-puberty”** from 2-24 weeks, which has a known impact on brain development, masculinization, and promotion of social behaviors.
 - ~ 175 boys with 47,XXY, ages 0-5 years, 11 months grouped by Rx: EHT or No-T.
 - **EHT group scored significantly higher on expressive language** than No-T group in <12 mo, 24–35 mo, 36–47 mo, and 60–71 mo, (p=0.09, p=0.0002, p=0.009, p=0.02, respectively).
 - **EHT group scored significantly better on auditory comprehension** than the No-T group in <12 mo and 24–35 mo (p=0.02 and p=0.05, respectively).

Samango-Sprouse C, *et al.* The effect of early hormonal treatment (EHT) on expressive and receptive language capabilities in boys with 47,XXY (Klinefelter syndrome) during infancy and early childhood. *Genet Med.* 2021 Jun; 23(6):1017-1022. PMID: 33627828



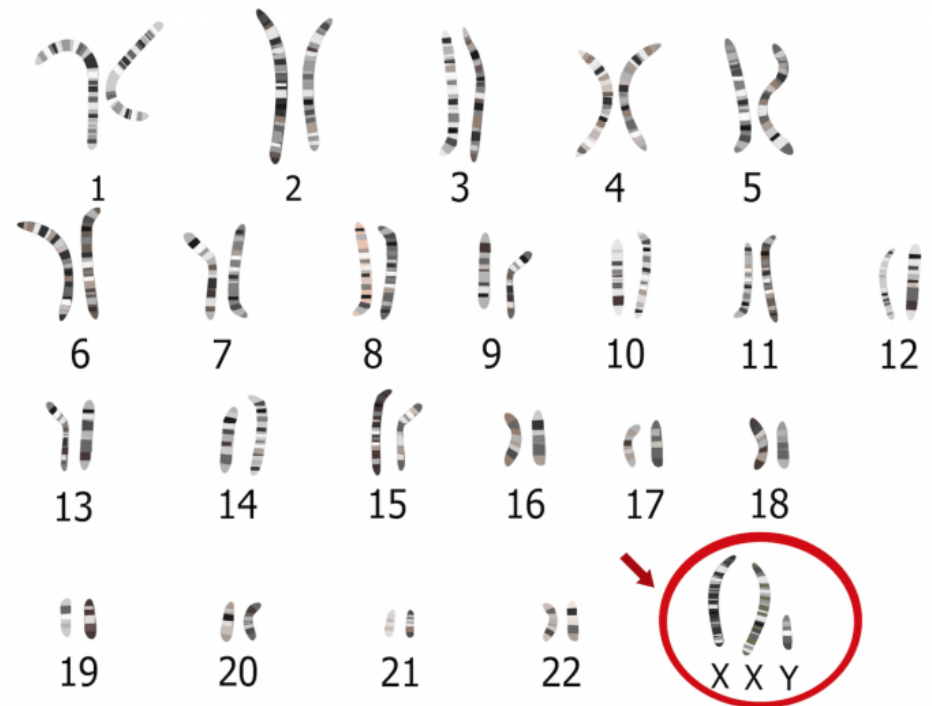
Important points: Klinefelter syndrome

- *Points to know*

- **KS is common**
 - *More common than Down syndrome*
- **KS is underdiagnosed**
- *Neonatal dx of KS is more common now with NIPT*
- **Low dose testosterone in infancy may improve outcome**

- *Things to do*

- **Follow up positive NIPT with a karyotype**
- **Order a karyotype in babies with small penis +/- bilat. undescended testes, esp. undescended at 12 mo**
- **Refer promptly to Genetics and Endocrinology**



Achondroplasia: the most common skeletal dysplasia

- » Most common skeletal dysplasia
 - ~ Prevalence 1 in 15-25,000
 - ~ 80% of cases are sporadic
 - ~ 100% penetrance
- » Autosomal dominant trait caused by **activating** variant in ***FGFR3***
- » Clinical features: short limbs, “rhizomelia” disproportionate short stature, “trident hand”, macrocephaly
- » Most infants have hypotonia, motor delay, sleep disordered breathing, snoring.
 - ~ Many have ankle clonus & hyperreflexia



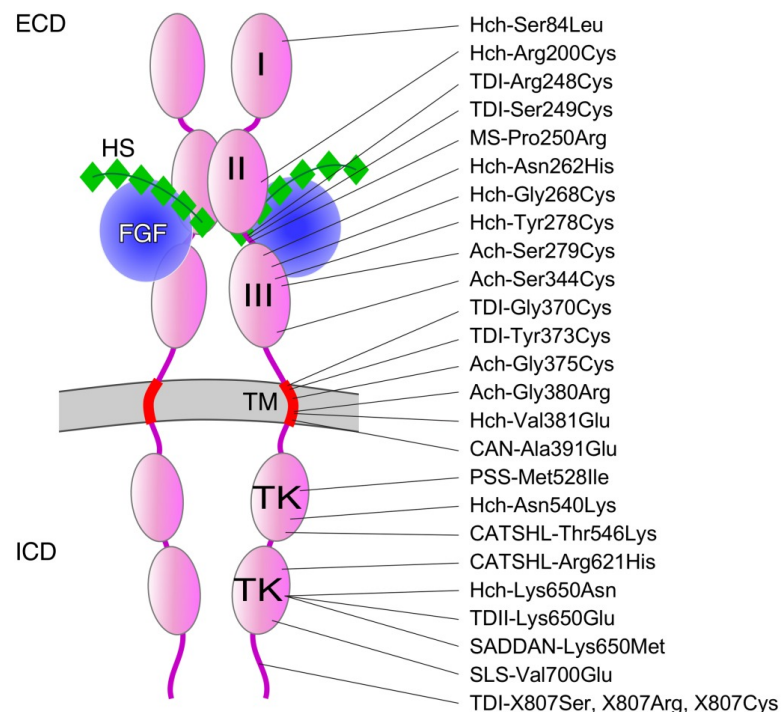
Pauli RM. Achondroplasia: a comprehensive clinical review. Orphanet J Rare Disease. 2019;14(1):1. PMID 30606190



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FGFR3 variants cause Achondroplasia

- » **FGFR3 negatively regulates bone growth.**
- » Achondroplasia is caused by an **activating variant**, c.1138G>A, in **FGFR3**
- » Other *FGFR3* variants cause common skeletal disorders
 - ~ Skeletal dysplasias
 - Hypochondroplasia
 - Thanatophoric
 - ~ Craniosynostosis syndromes
 - Crouzon syndrome
 - Muenke syndrome



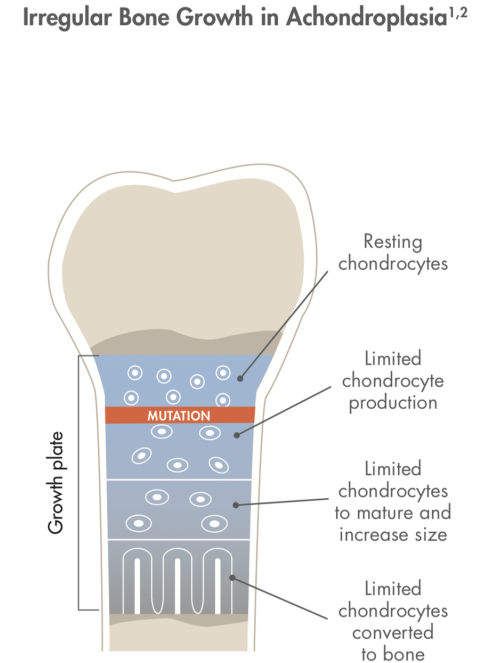
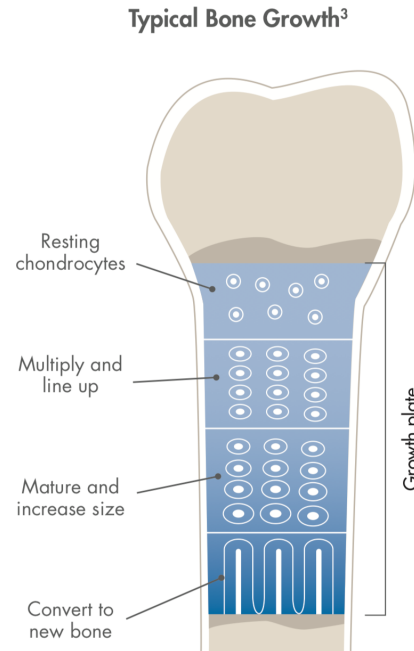
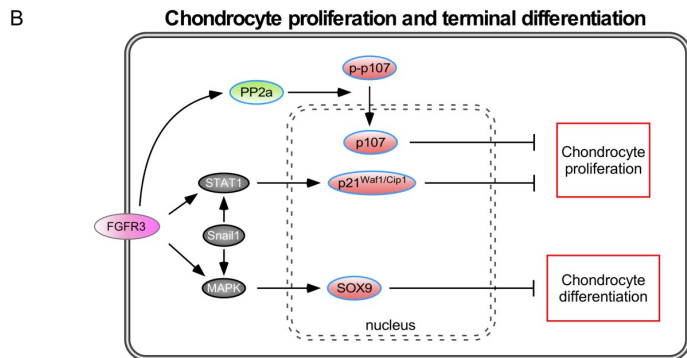
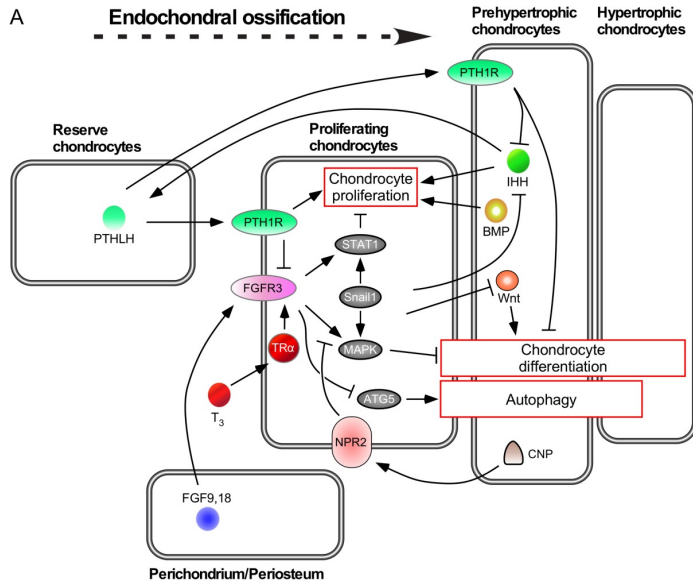
Ach, Achondroplasia
CAN, Crouzon syndrome with Acanthosis Nigricans
CATSHL, Camptodactyly, Tall stature, and Hearing loss
Hch, Hypochondroplasia
MS, Muenke syndrome
PSS, proportional short stature
SADDAN, Severe Achondroplasia with Developmental Delay and Acanthosis Nigricans
SLS, Spider lamb syndrome (*Ovis aries Fgfr3*)
TDI, Thanatophoric dysplasia type I
TDII, Thanatophoric dysplasia type II

Ornitz DM. Achondroplasia: Development, pathogenesis, and therapy. *Developmental Dynamics*. 2016;246(4):291-309



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FGFR3 inhibits bone growth



FGFR3 inhibits chondrocyte proliferation and differentiation

Ornitz DM. Achondroplasia: Development, pathogenesis, and therapy. *Developmental Dynamics*. 2016;246(4): 291-309



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Achondroplasia causes foramen magnum stenosis, cord impingement & central apnea

» Infants and toddlers are at highest risk of **spinal cord compression**, best identified on **T-2 weighted MRI** images.

~ **Sudden death in infancy**, 0.5-7.5%, due to acute or chronic cervical spinal cord and brainstem compression and central apnea

~ **Acute life-threatening events** <1y, are **common**

- 18/477 (**3.8% in all, 5.5% in males**, Legare 2021)
- Present as apneic events or sz
- **Often in car seats** (11/18)

» Foramen magnum dimensions are reduced in infancy, enlarge with age.

~ **Decompression surgery** varies from 4-43%.



Gross pathologic features from the craniocervical junction of the spinal cord in an infant with achondroplasia who died suddenly and unexpectedly. There is gross indentation of the cord as well as cystic lesions secondary to hypoxic damage.

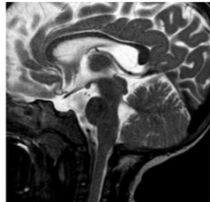
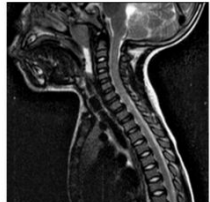
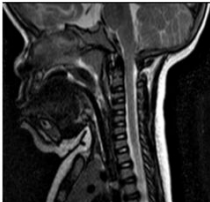

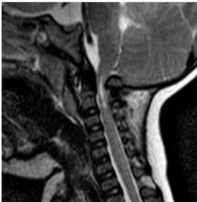
Pauli RM *et al.* Apnea and sudden unexpected death in infants with achondroplasia. *J Pediatr.* 1984;104:342–348
Legare JM, *et al.* Achondroplasia is associated with increased occurrence of apparent life-threatening events. *Acta Paediatr.* 2021 Jun;110(6):1842-1846. PMID: 33452838



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Achondroplasia Foramen Magnum Score

- » **No evidence based guidelines** exist but **AAP consensus expert opinion** advocates neuroimaging (CT or MRI) and polysomnography for all infants with achondroplasia
- » Cheung (2021) imaged 36 infants with achondroplasia to develop a **foramen magnum score**, and correlated the score with clinical course. **Only 2/36 (5.6%) had no evidence of foramen magnum narrowing**, AFMS0. 36.1% had AFMS1.
- » **Clinical exam and sleep studies POORLY predict effects of spinal cord compression.**
 - ~ 9/36 (25%) infants required neurosurgery, 8/9 had FM decompression and all were AFMS3-4.
 - ~ Neurological examination was normal in 34/36 (94%) patients, 2 abnormal pts both required surgery.

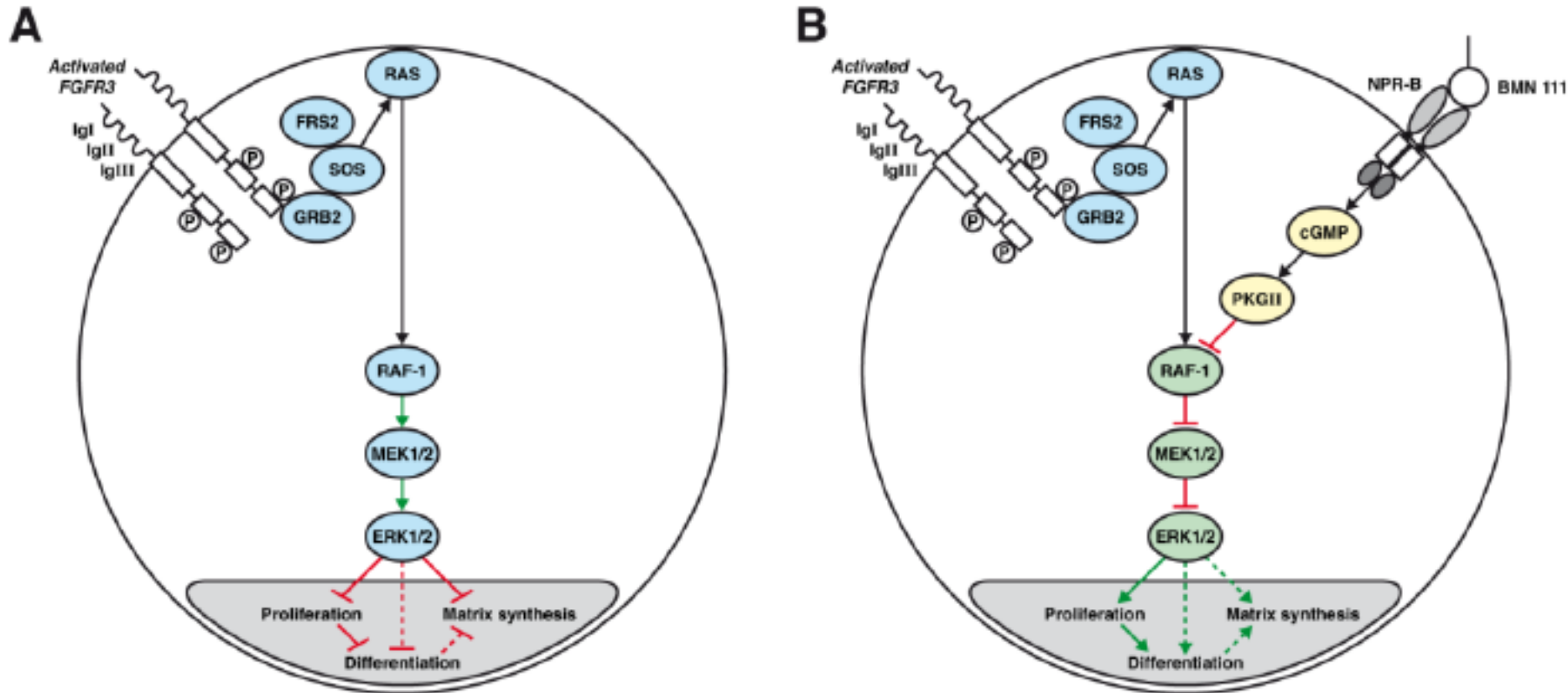
AFMS0	AFMS1	AFMS2	AFMS3	AFMS4
Normal foramen magnum	Constitutional narrowing of the foramen magnum with preserved CSF (no cord distortion)	Narrowing of the foramen magnum with loss of CSF space surrounding the cord	Loss of the CSF space with cord compression	Cord compression and signal changes (Myelomalacia)
				

- » Disordered sleep breathing in 31/35 (88.5%). **Severity of OSA correlated with AFMS scores**
- » **AFMS3-4 is common: Spinal cord changes were common, 18/36 (50%; 14% AFMS4)**
- » **Clinical exam and sleep study are poor screening tests** for severe cord stenosis and would have missed 5 infants with AFMS3-4.

Cheung MS, *et al.* Achondroplasia Foramen Magnum Score: screening infants for stenosis. Arch Dis Child. 2021 Feb; 106(2):180-184. PMID: 32883660



C-natriuretic peptide analog (BMN111) blocks the effect of activated FGFR3

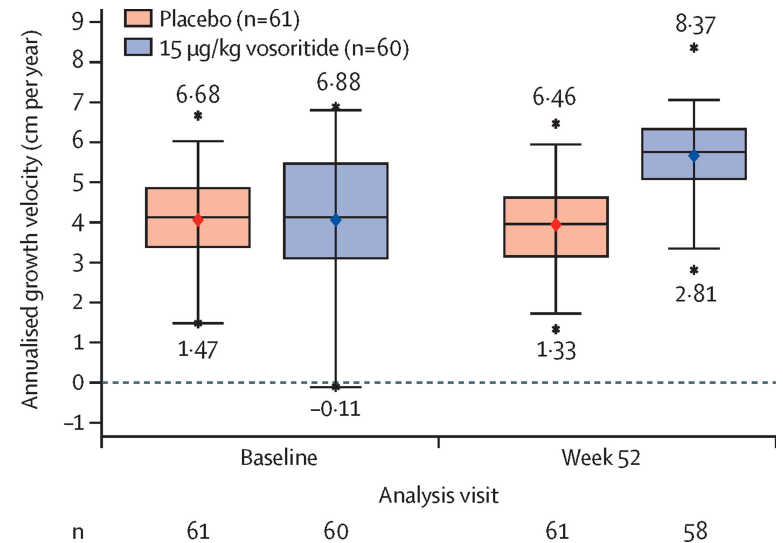


Ravi Savarirayan, *et al.* Once-daily, subcutaneous vosorotide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *The Lancet.* 2020; 396(10252):684–692



Vosoritide increases growth in Achondroplasia

- » Vosoritide, a **biologic analog of C-type natriuretic peptide** (BMN111), is a potent stimulator of endochondral ossification and reduces the effect of overactive *FGFR3*.
- » Phase III clinical trial for ages 5-18 has been completed: 24 sites in 7 countries
 - ~ 121 children with achondroplasia participated in a randomized double blind trial
 - ~ Annualized growth velocity was **1.57 cm/year more** in the vosoritide group (95% CI [1.22–1.93]; two-sided $p < 0.0001$).



Professor Ravi Savarirayan,
Group leader, Skeletal Biology and
Disease
Murdoch Children's Research Institute



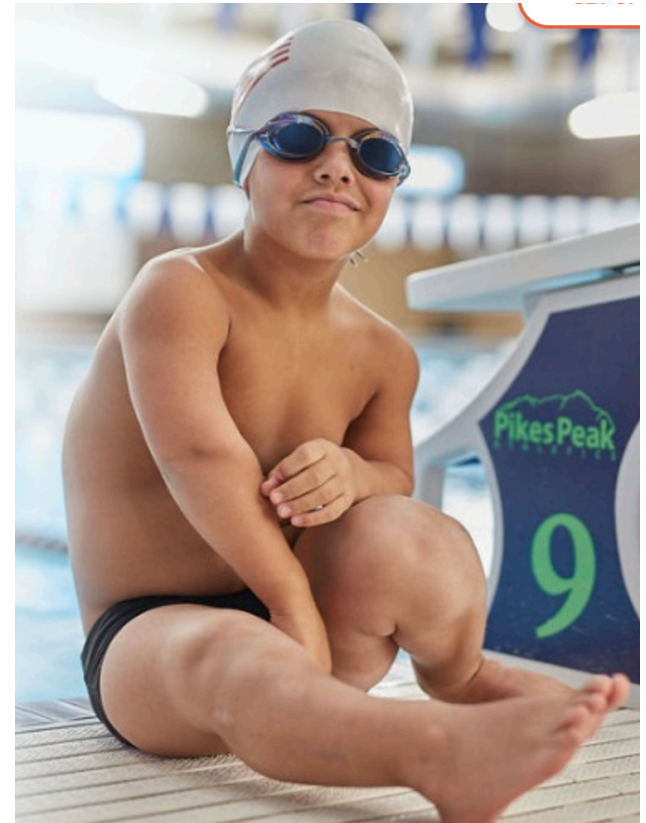
Ravi Savarirayan, *et al.* Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *The Lancet*. 2020; 396(10252):684–692



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Vosoritide treatment for Achondroplasia is pending FDA approval

- » USA: Vosoritide (BioMarin) is pending FDA approval based on complete data from 5-18 y cohort and some data from 2-5 y cohort.
- » Europe: On June 25, 2021, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending marketing authorization for vosoritide to treat achondroplasia in children **from the age of 2** until growth plates are closed.
 - ~ Final decision from European Commission expected in Q3 2021
- » Ascendis Pharma and others are developing similar CNP analog therapies.



Ravi Savarirayan, *et al.* Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *The Lancet.* 2020; 396(10252):684–692



Important points: Achondroplasia

- *Points to know*

- *An **activating FGFR3** variant inhibits growth*
- ***Foramen magnum stenosis** contributes to an increased risk of **sudden death and ALTE** in infants and toddlers*
- ***50%** of affected infants have **cord changes on T2 weighted MRI***
- *Clinical exam and polysomnography alone are **poor predictors** of spinal cord compression*
- *Sleeping disordered breathing is common*
- *Soon **C-type natriuretic peptide analogs** will be available to treat achondroplasia.*

- *Things to do*

- *Follow AAP guidelines*
- *Image craniocervical junction with CT or MRI in all infants with achondroplasia*
- *Order polysomnography*
- *Examine for severe hypotonia, asymmetric reflexes or hyperreflexia*
- *Advise parents about need for head support esp. when in a car seat. Avoid soft back seats.*
- *Refer promptly to Genetics*



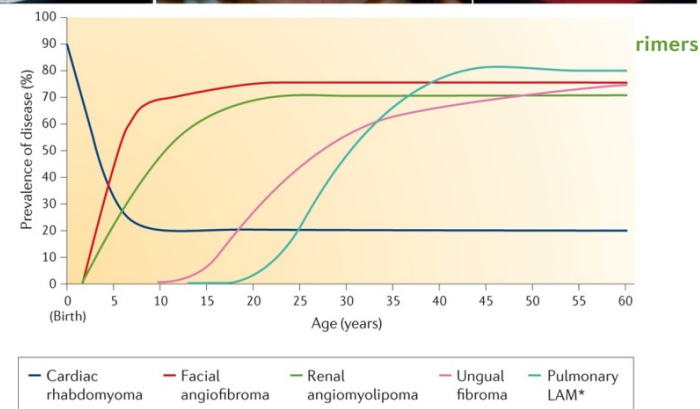
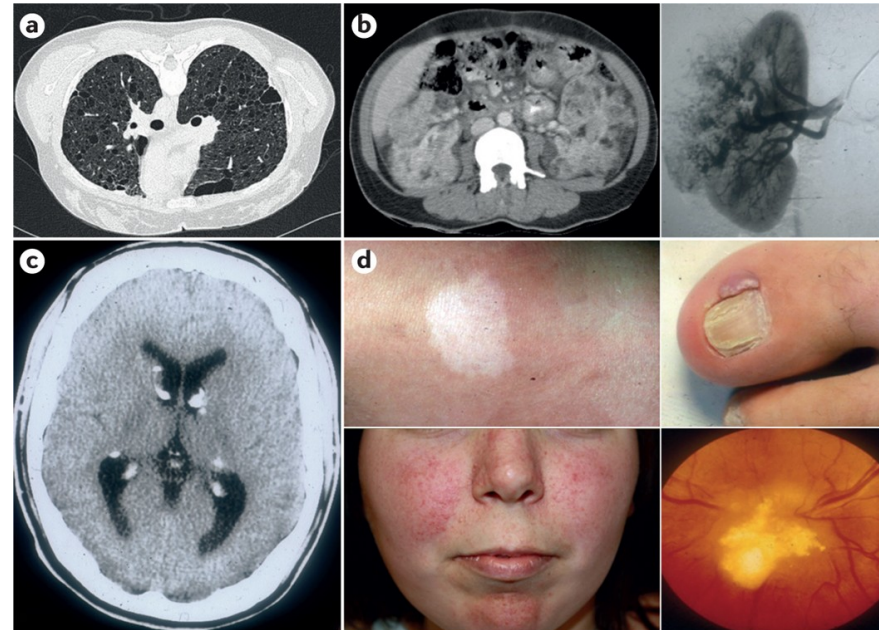
Hoover-Fong J, et al; COMMITTEE ON GENETICS. Health Supervision for People With Achondroplasia. Pediatrics. 2020 Jun;145(6):e20201010. PMID: 32457214



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Tuberous sclerosis complex (TSC)

- » Prevalence ~**1:6,000** newborns. 50,000 are affected in the USA
- » Loss-of-function mutations in tumor suppressors **TSC1** or **TSC2**, which are negative regulators of the **mTOR pathway**
 - ~ **2/3 de novo**, some of which are mosaic; 1/3 familial
- » Phenotype is **variable**, even within the same family
 - ~ TSC1 disease is generally less severe.
 - ~ Usually benign tumor growths in kidney, heart, lung, eyes, skin, brain
- » Characteristic lesions in the brain
 - ~ **Cortical tubers** and ventricular **subependymal nodules**, that may progress to **subependymal giant cell astrocytomas (SEGAs)**
- » Neurological manifestations
 - ~ Epilepsy, neurodevelopmental delay, and TSC-associated neuropsychiatric disorders (TANDs): **intellectual disability**, **autism spectrum disorder (ASD)**
- » **TSC is the most common genetic cause of pediatric epilepsy**
 - ~ ~**85% develop seizures**, usu. within the first year
 - ~ **1/3** of infants with TSC develop **infantile spasms**
 - ~ **2/3** develop **refractory epilepsy**, **twice the rate** in the general epilepsy population
 - ~ **Uncontrolled sz activity or early onset of sz before 6 months aggravates cognitive comorbidities**
 - ~ **Immediate seizure management** after or **ideally before epilepsy onset** is crucial for normal cognitive development



Henske EP, et al. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016 May 26;2:16035. PMID: 27226234.

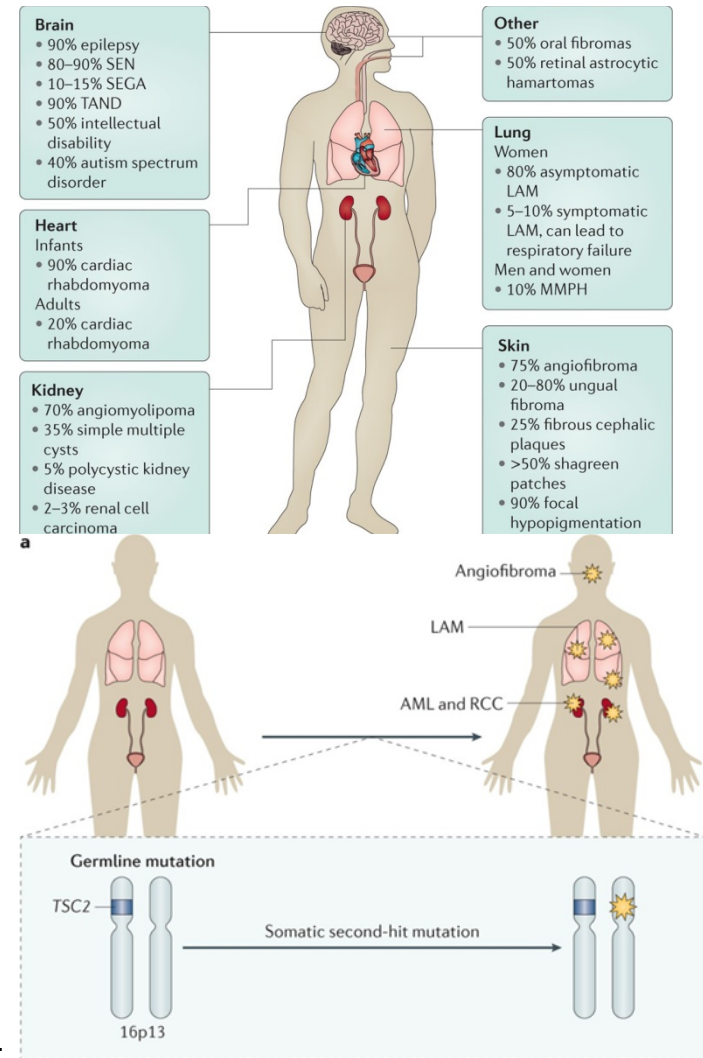
Nature Reviews | Disease Primers



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TSC tumors need 2nd hit

- » TSC lesions are **more numerous with time**
- » Follow the Knudson “two-hit” hypothesis
- » Somatic mutations in either *TSC1* or *TSC2*, result in the loss of wild-type alleles
- » These have been detected in different TSC neoplastic lesions and to a lesser extent in cortical tubers
- » Treatment to reduce the number of second hits will likely ameliorate disease.

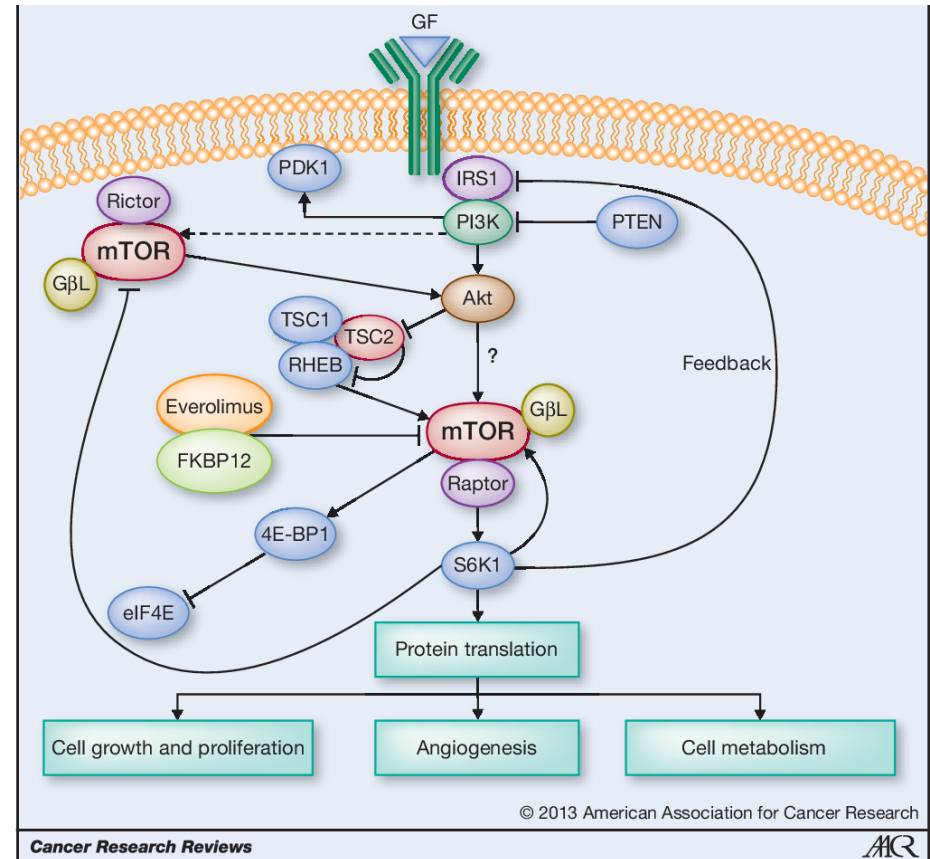


Henske EP, et al. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016 May 26;2:16035. PMID: 27226234.



mTOR pathway is activated in TSC

- The TSC protein complex, which includes *TSC1* and *TSC2*, normally inhibits mTOR (mechanistic Target Of Rapamycin) complex 1 (mTORC1)
- mTORC1 controls and mediates cell growth, proliferation, autophagy and protein and lipid synthesis
- mTOR inhibiting agents, such as **Everolimus**, have been approved by the FDA for treatment of renal, brain and other TSC-associated tumors



Henske EP, et al. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016 May 26;2:16035. PMID: 27226234



Everolimus, an mTOR inhibitor, treats tumors associated with TSC

» A retrospective multicenter study in 12 sites in Germany, reported 17 children with TSC, 0-6 yrs, treated with **Everolimus**, mTOR inhibitor therapy.

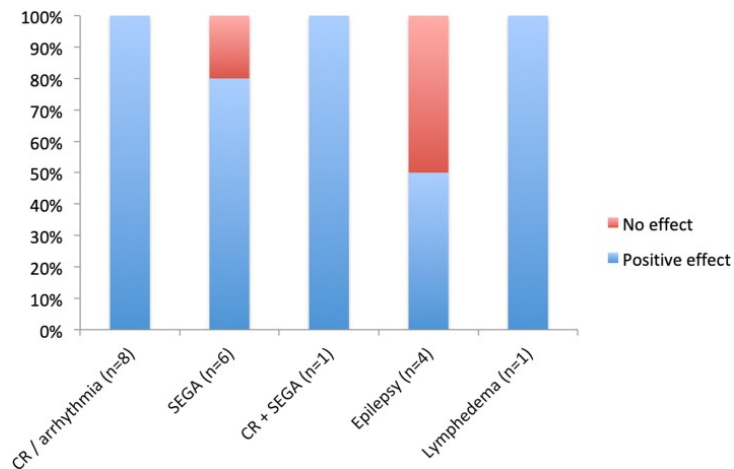
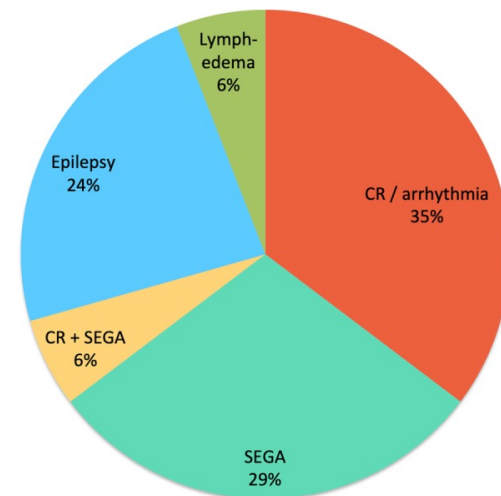
~ Median age at Rx: **5 mo.** (range 0-19)

» Indications:

- ~ Cardiac rhabdomyoma (6)
- ~ Subependymal giant cell astrocytomas (SEGA, 5)
- ~ Both (1)
- ~ Refractory epilepsy (4)
- ~ Congenital focal lymphedema edema (1)

» Results:

- ~ **14/17 patients benefited from therapy**
 - decrease in size of SEGA (4/5) and/or cardiac rhabdomyoma,
 - reduced sz frequency
 - regression of lymphedema, improvement in arrhythmia.
- ~ **In the epilepsy group, 2/4 continued to have intractable epilepsy**



Saffari A, *et al.* Safety and efficacy of mTOR inhibitor treatment in patients with tuberous sclerosis complex under 2 years of age - a multicenter retrospective study. *Orphanet J Rare Dis.* 2019 May 3;14(1):96. PMID: 31053163



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Treating EEG changes prevents sz in TSC



Long-term, prospective study evaluating clinical and molecular biomarkers of epileptogenesis in a genetic model of epilepsy – tuberous sclerosis complex.

- » In the majority of TSC-related sz, **clinical sz (CS)** are preceded by asymptomatic **epileptiform activity (EA)** on EEG, followed by **asymptomatic electrographic sz (ES)**
- » EPISTOP prospective study in 10 sites: 94 TSC infants, ≤ 4 mo, without CS or ES on baseline EEG, had monthly video EEG and received **vigabatrin** in a double blinded Randomized Controlled Trial (RCT, 6 sites) or Open Label Trial (OLT, 4 sites)
 - ~ Infants in OLT were treated **EITHER** as conventional antiepileptic treatment started after first ES or CS (2 sites) **OR** as preventive therapy after EA but *before* CS (2 sites)
- » In **54 subjects, EA was identified before seizures**: 27 (13 allocated to preventive Rx) in RCT, 27 in OLT.
- » RESULTS: In a pooled analysis of both RCT and OLT:
 - ~ **In infants who developed CS**, median CS onset was **day 614** in infants **who received preventive therapy** and day 124 in infants with conventional therapy
 - ~ **Patients in the preventive group were 3x more likely to remain free of clinical sz** (46% vs 15% in RCT, 50% vs 7% in OLT, $p=0.011$)
 - ~ **At 24 mo, preventive treatment reduced the risk of CS** (odds ratio [OR] = 0.21, $p = 0.032$), **drug-resistant epilepsy** (OR = 0.23, $p = 0.022$), and **infantile spasms** (OR = 0, $p < 0.001$).
- » CONCLUSION: Preventive treatment with vigabatrin was safe and modified the natural history of seizures in TSC, reducing the risk and severity of epilepsy.

Kotulska, *et al*; EPISTOP Investigators. Prevention of Epilepsy in Infants with Tuberous Sclerosis Complex in the EPISTOP Trial. *Ann Neurol*. 2021 Feb;89(2):304-314. PMID: 33180985



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Important points: Tuberous Sclerosis

» Points to know:

- ~ TSC is a multisystem disorder with variable but often serious and debilitating sequelae
- ~ TSC1 and TSC2 normally **inhibit the mTOR pathway**
- ~ **Pathogenic LOF variants in TSC1 and TSC2 increase activity in the mTOR pathway.**
- ~ **Seizures in TSC precede and likely contribute to the etiology of intellectual disability and autism in TSC.**
- ~ Preventing sz reduces TSC-associated neuropsychiatric disorders
- ~ mTOR pathway inhibitors (**Everolimus**) and the **antiepileptic vigabatrin**, can ameliorate tumors and prevent seizures and neurocognitive disorders in TSC

» Things to do:

- ~ **Refer** infants with suspected TSC or family hx of TSC for prompt genetic diagnosis and neurologic and neurocognitive assessments
- ~ **Follow surveillance protocols** and establish baseline status of renal function, brain MRI, video EEG, renal US, echocardiogram
- ~ Let families know the benefit of **early therapy** to treat tumors and prevent seizures



Special thanks to Dr. Stephen Ashwal, a true expert on tuberous sclerosis and so much more



Klippel-Trenaunay syndrome: Sporadic vascular malformation, limb asymmetry, overgrowth

Clinical phenotype:

Disproportionate overgrowth disturbance with cutaneous capillary, lymphatic, and venous malformations.

Variable phenotype: usu. affects **lower extremities** but also **upper extremities**, can be **bilateral**.

Usually **focal** and spares the craniofacial region.

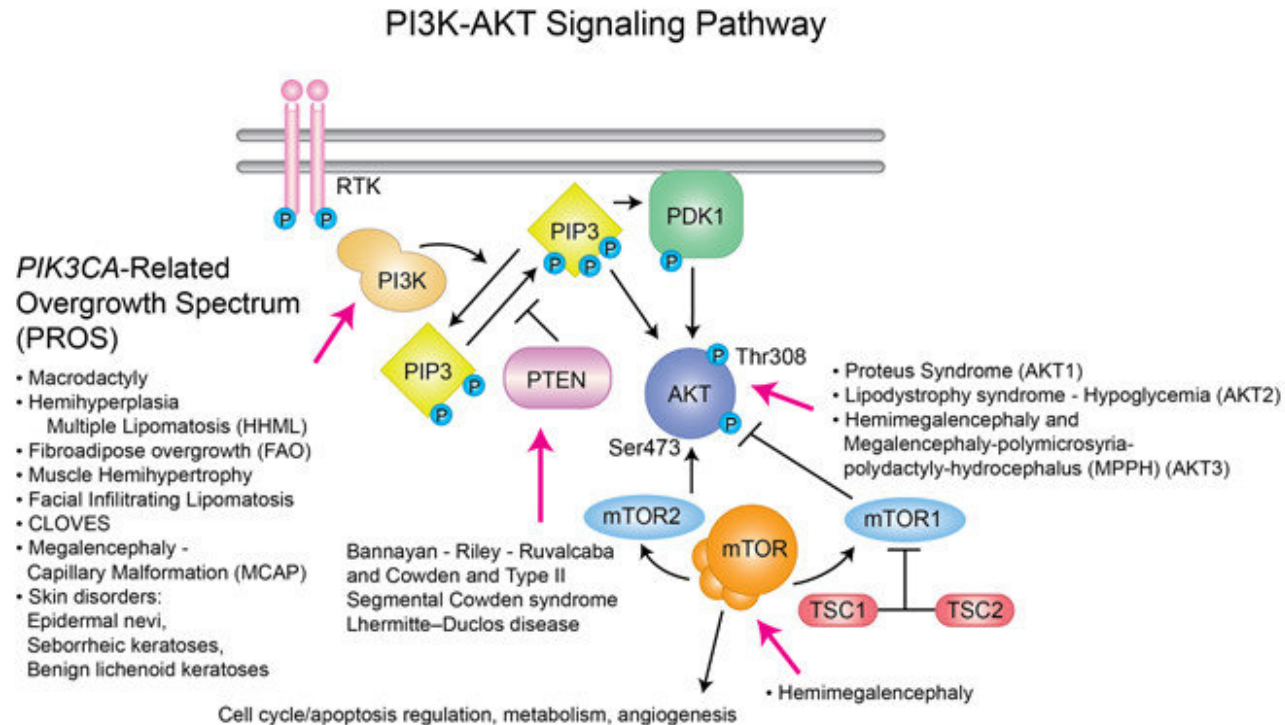
Capillary malformation is often **sharply circumscribed, violaceous** on lateral aspect of the affected extremity.

May develop hemorrhagic and clear (lymphatic) vesicles on its surface



Klippel-Trenaunay syndrome is part of the PROS group of disorders

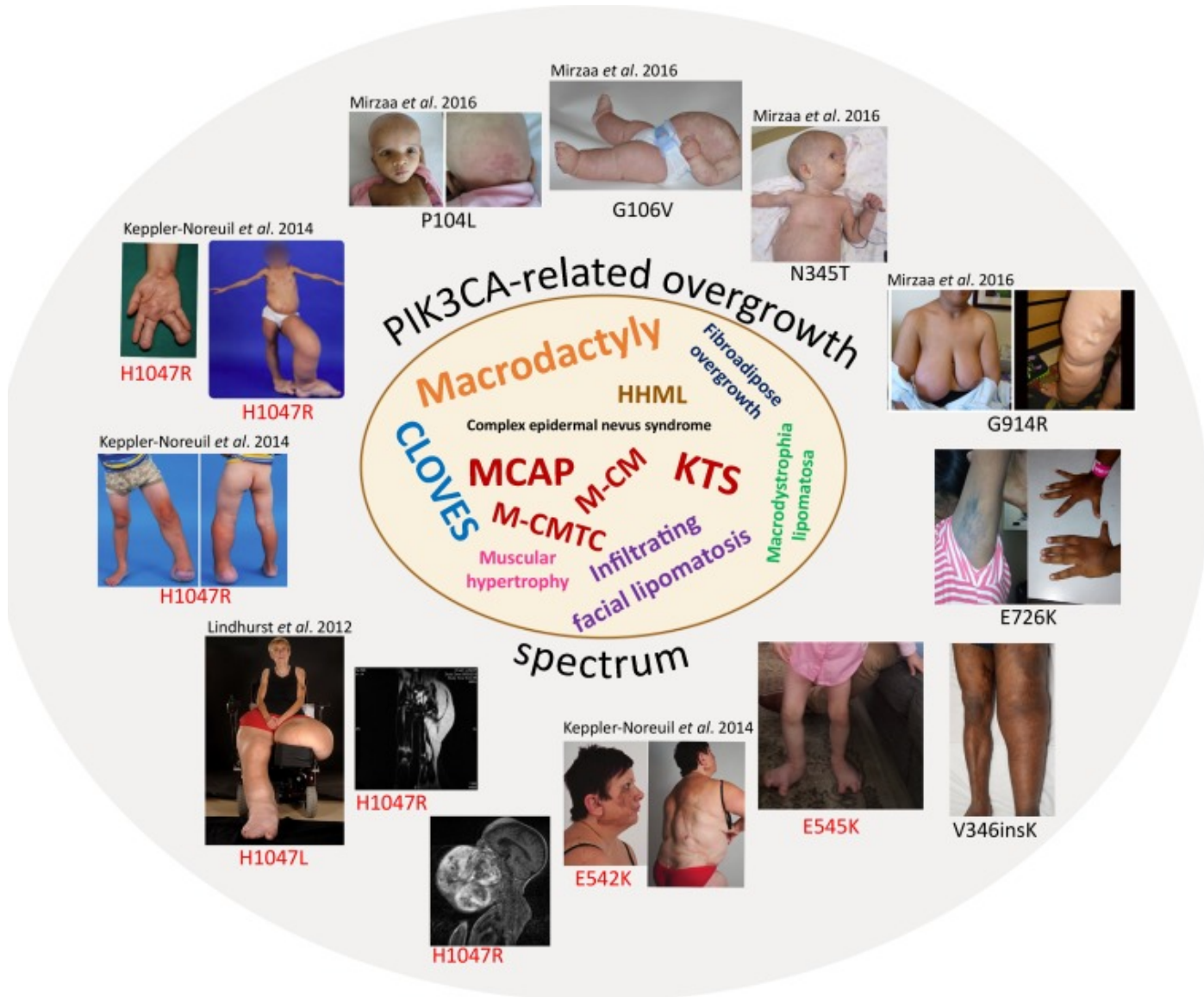
- » **PIK3CA-Related Overgrowth clinical Spectrum (PROS)**
- » Due to *postzygotic somatic activating* mutation during embryogenesis in **PIK3CA**: phosphatidylinositol-4,5 bisphosphate 3-kinase catalytic subunit alpha
- » **Gain-of-function variants activate downstream mTOR growth pathway.**
- » **Pathogenic variant present only in affected tissue**
- » Test for *PIK3CA* variants in *affected tissue* and un-affected tissue or blood for comparison



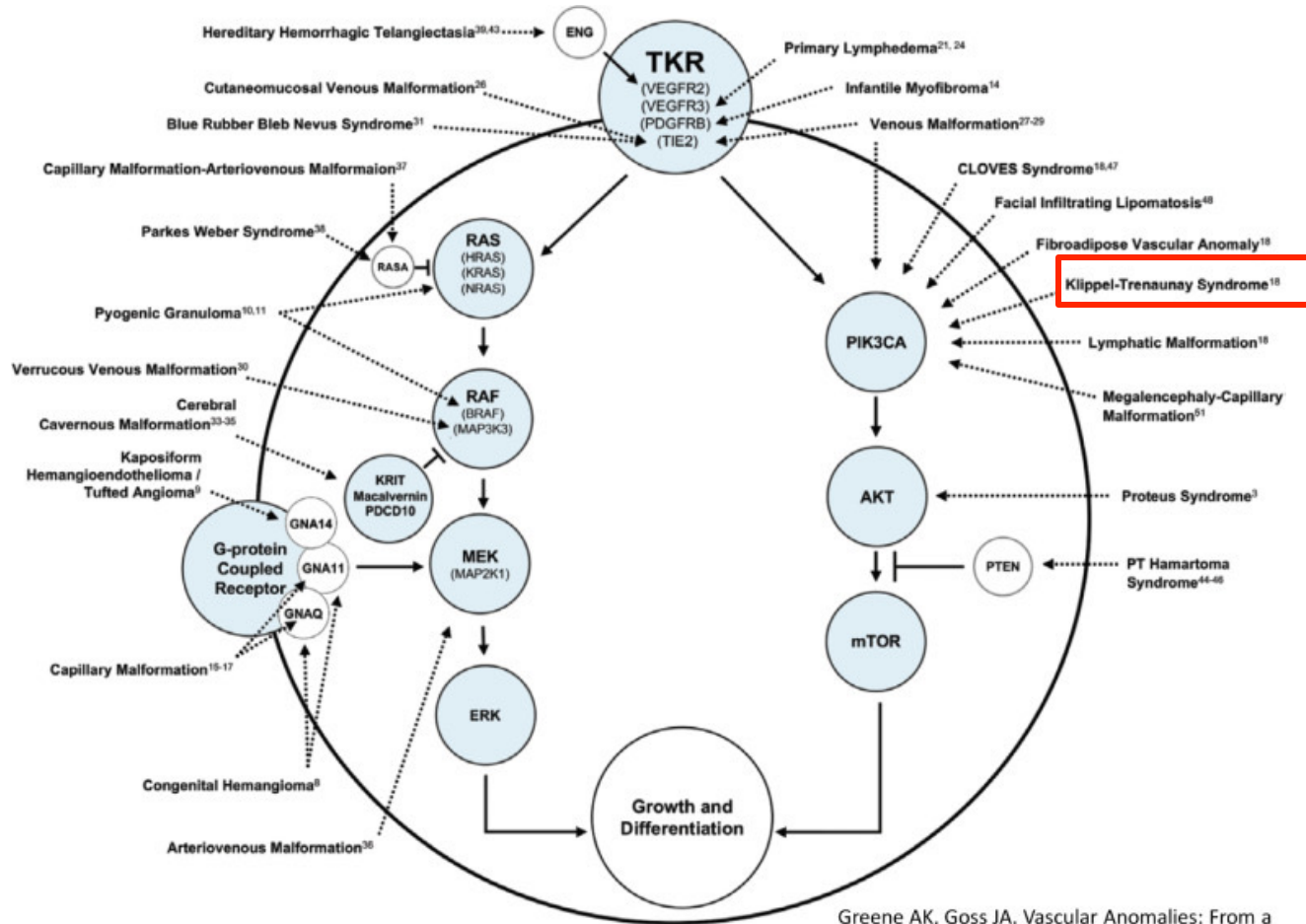
Keppler-Noreuil KM, *et al.* PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *Am J Med Genet A.* 2015 Feb;167A(2):287-95. PMID: 25557259



The PROS phenotype (and disorder name) varies with the affected tissue



Other vascular malformations are caused by genes in related pathways



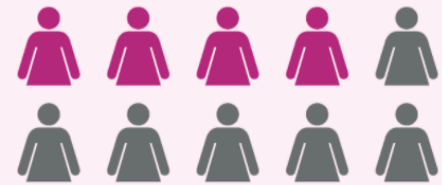
Greene AK, Goss JA. Vascular Anomalies: From a Clinicohistologic to a Genetic Framework. *Plast Reconstr Surg* 2018;141:709e.



Alpelisib [PIQRAY] prolongs survival in patients with *PIK3CA*+ HR+, HER2- Breast Cancer

- » In the SOLAR-1 randomized trial, alpelisib-fulvestrant prolonged progression-free survival in advanced breast cancer
- » 572 patients were randomized, including 341 with tumor-tissue *PIK3CA* mutations.
- » **In the *PIK3CA*+ cancer group**, at median follow-up of 20 mo., progression-free survival was **11.0 mo** (95% CI 7.5-14.5) **in the alpelisib-fulvestrant group**
- » **In the placebo-fulvestrant group**, it was **5.7 months** (95% CI, 3.7-7.4) in the (hazard ratio for progression or death, 0.65; 95% CI, 0.50 to 0.85; **P<0.001**)

PIK3CA Mutations



~40% of patients with hormone positive (HR+), HER2 negative (HER2-) breast cancer harbor *PIK3CA* activating mutations, the most frequent mutation within luminal breast cancer.¹

PIK3CA mutations are a key driver of breast cancer and have typically been associated with a poor prognosis.²

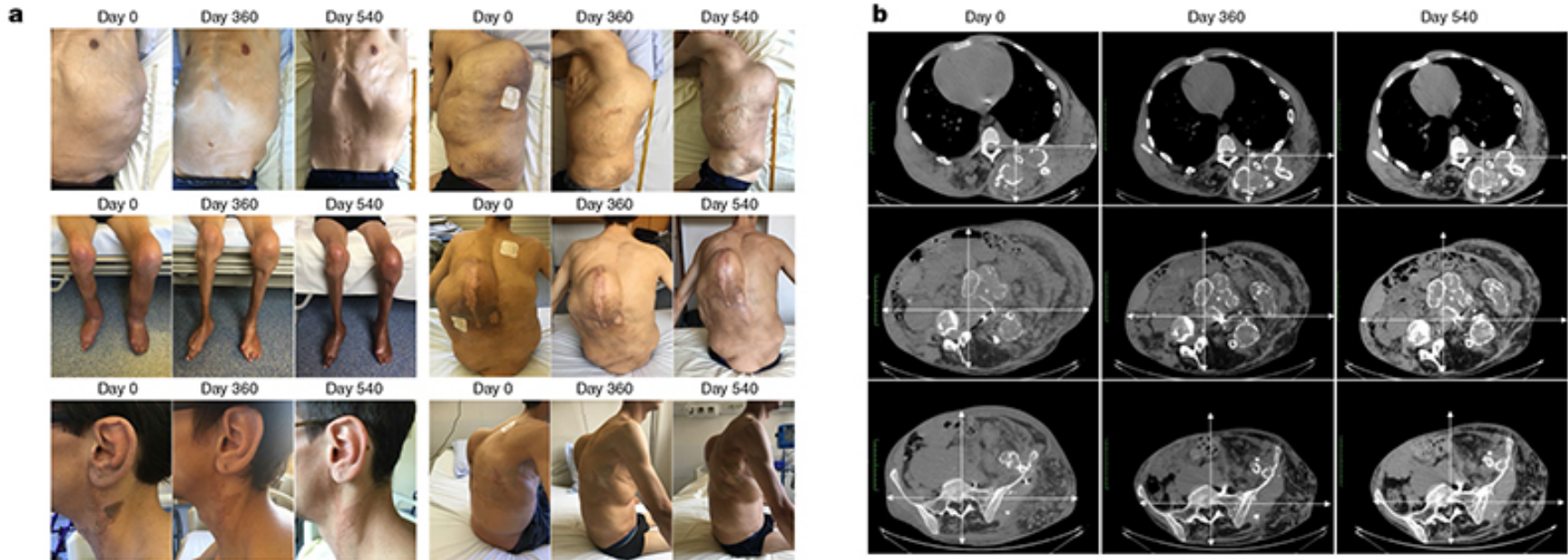
André F, *et al.*; SOLAR-1 Study Group. Alpelisib for *PIK3CA*-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. *N Engl J Med.* 2019 May 16;380(20):1929-1940. PMID: 31091374



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Alpelisib is also effective in PROS

- » Alpelisib, an alpha-specific selective PI3K inhibitor, stabilizes disease severity and diminishes symptoms in PROS.
 - ~ Alpelisib (PIQRAY) is an FDA-approved drug for breast cancer



- » PROS patients >2 years of age are eligible for Alpelisib treatment in a managed access program or a clinical trial, sponsored by Novartis.
 - ~ <https://clinicaltrials.gov/ct2/show/NCT04085653>

Venot Q, *et al.* Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature*. 2018 Jun;558(7711):540-546. PMID: 29899452



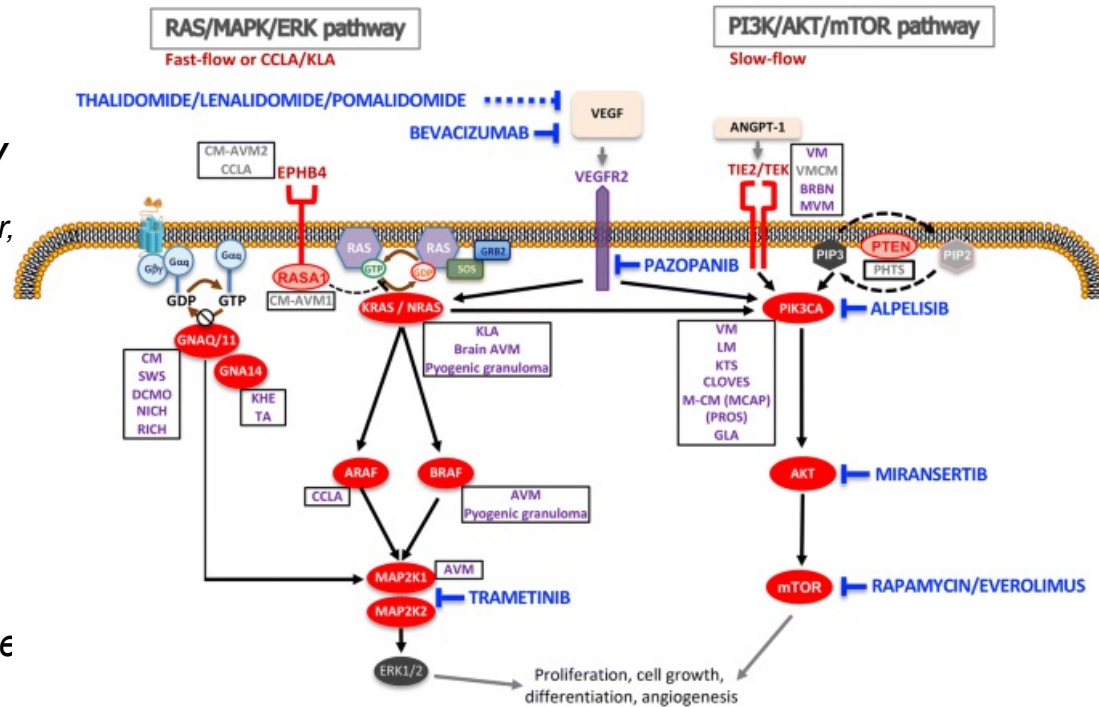
Important points: Klippel-Trenaunay syndrome

• Points to know

- **KTS is caused by a somatic activating mutation in PIK3CA** that occurs during embryogenesis.
 - Other overgrowth syndromes are caused by somatic variants in different genes in related pathways.
- It is **only present in some tissues & usually not detectable in blood**
- KTS is a PIK3CA related overgrowth disorder, PROS.
- **Alpelisib [PIQRAY] prolongs survival in PIK3CA+ breast cancer and reduces overgrowth in PROS**
 - Anticipate treatment for other overgrowth disorders

• Things to do

- **Refer patients with KTS or any vascular malformation or overgrowth disorder for genetic evaluation and tissue testing**
- **Talk to patients with KTS about the clinical trial for treatment with Alpelisib**



Summary

- » Anticipate and take opportunities to treat sequelae in these common genetic disorders
 - ~ Down syndrome
 - ~ Klinefelter syndrome
 - ~ Achondroplasia
 - ~ Tuberous sclerosis
 - ~ Klippel-Trenaunay syndrome
- » Active management by pediatricians can expedite care and prevent severe outcomes in these disorders.
- » Refer often and early



Thank you!

Reach out to me with questions or referrals at rclark@llu.edu

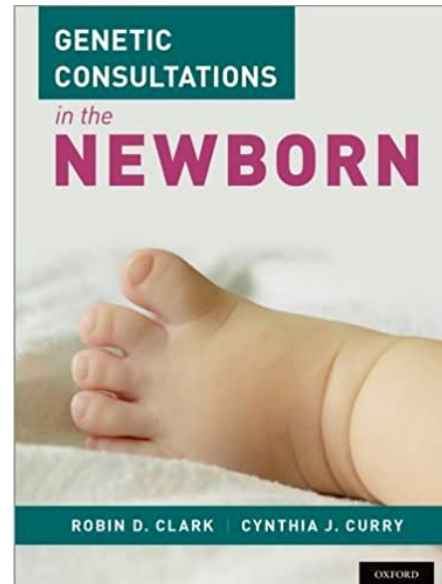
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For more up-to-date genetic content:

Genetic Consultations in the Newborn, published by Oxford University Press

Look for the monthly Genetics Corner case report in Neonatology Today: www.neonatologytoday.net



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