TSC
CANADA

Tuberous Sclerosis Complex

Tuberous Sclerosis Complex

- Incidence 1:5800
- Affects 1-2 million people worldwide
  - Over 3500 in Canada alone
- Genetic disorder
  - Mutations in genes TSC1 and TSC2
- Multiorgan benign tumors throughout the body
  - Brain, kidneys, skin, lungs, liver, heart, eyes
- Cerebral manifestations:
  - Subependymal nodules (SENs)
  - Cortical and subcortical tubers
  - Subependymal giant cell tumours (SGCTs)

TSC CANADA

A Patient's Journey with TSC

Patient age at diagnosis	Prenatal / early infancy (< 24 months)	Early childhood (< 5yrs)	Teenagers (5–18 yrs)	Adults (> 18 yrs)	Adults (> 40 yrs)

Cardiac rhabdomyomas

Brain tumors (e.g., SEGA) / seizures / behavioral issues / mental disabilities

Dermatological manifestations
Hypomelanotic macules or "ash leaf spots" at birth, facial angiofibromas, forehead plaque or Shagreen patch

Retinal hamartomas

Renal or liver AMLs

LAMs

IMPORTANT TO NOTE:
Not all of these manifestations will occur in every person affected by TSC

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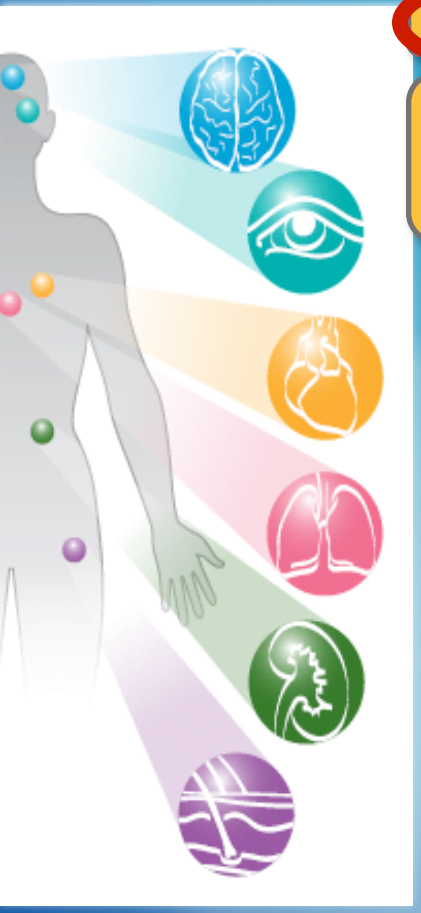

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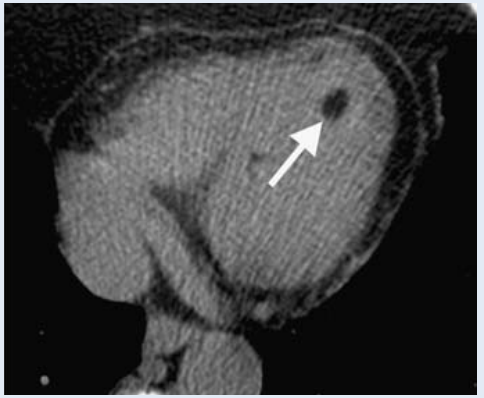
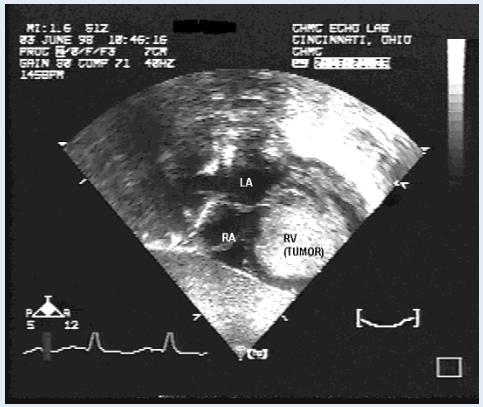
Cardiac Rhabdomyomas

- Present in 50 – 70% of infants born with TSC
- Although benign, their position within critical areas in the heart may lead to lethal arrhythmias and heart failure
- Usually detected *in utero* or during the first year of life
- Often regresses/disappears later in life



Cardiac rhabdomyoma: single (50% chance of TSC) or multiple (100% TSC)



1. Crino. *New Engl J Med* 2006;355:1345-56.

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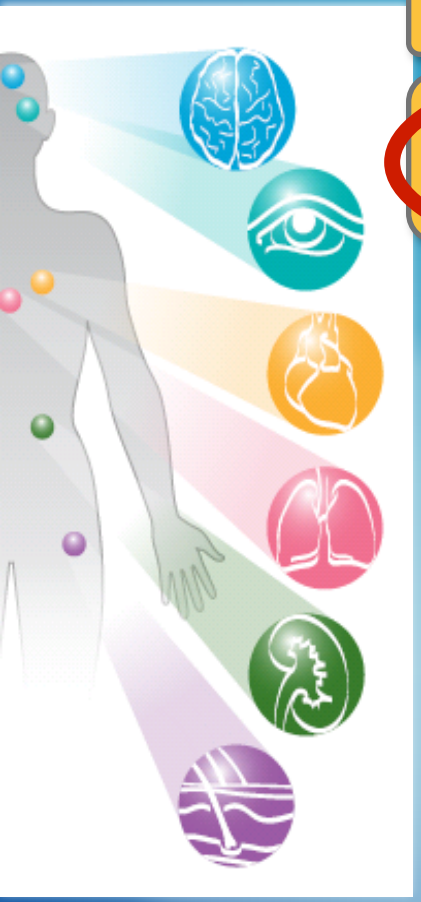

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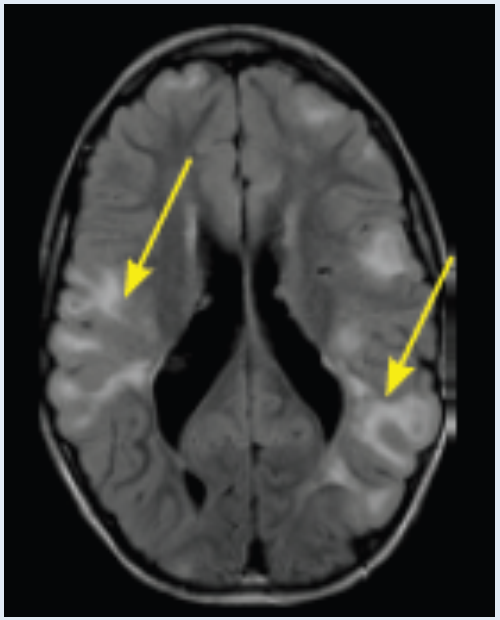
Neurologic Symptoms of TSC:
Cortical Tubers

- **Cortical tubers** are collections of dysmorphic neurons, large astrocytes, and giant cells[1,2]
- **Epilepsy** occurs in over 90% of patients and is associated with the presence of cortical tubers[2]
  - 33% will have infantile spasms[3]
  - Partial seizure is most common type of seizure[4]
  - 37% will have generalized seizures[4]

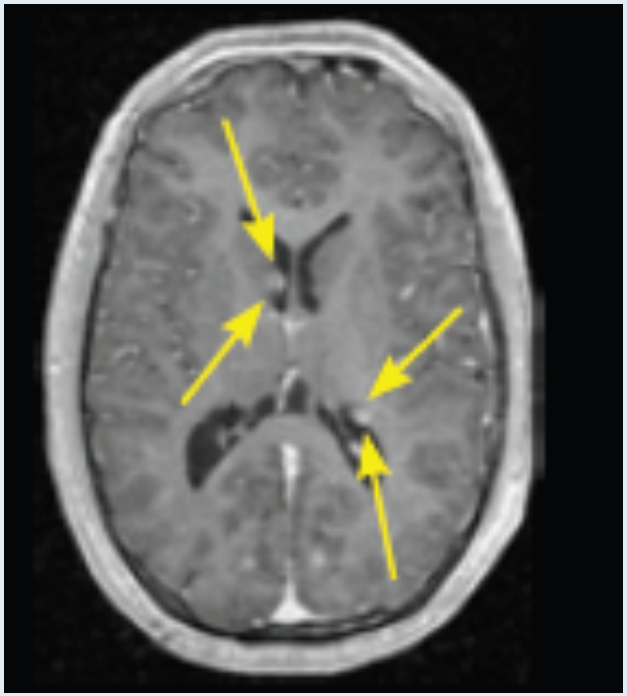


1. Crino. *N Engl J Med* 2006;355:1345-56; 2. Curatolo. *Eur J Paediatr Neurol.* 2002;6:15-23;
3. Wheless. *Epileptic Disord.* 2007; 9:353-412; 4. Chu-Shore. Epilepsia. 2009; 51:1236-41.

TSC CANADA

Neurologic Symptoms of TSC
Subependymal Nodules (SENs)

- SENs are benign tumors that develop along the ependymal lining of the lateral ventricles of the brain[1,2]
  - SENs usually remain dormant and do not cause symptoms
  - Some SENs may increase in size to become SGCTs

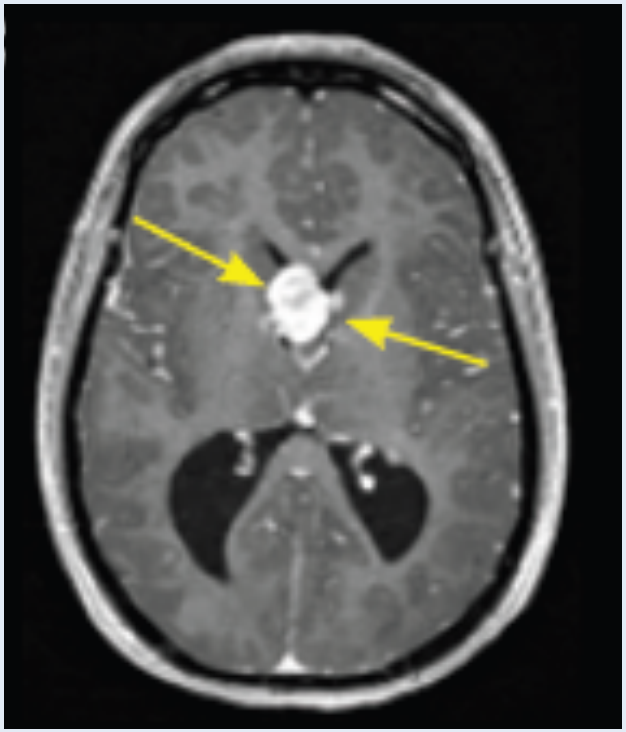


Numerous SENs distributed on the wall of the lateral ventricles

1. Yates. *Eur J Hum Genet 2006;14:1065-73.* 2. Crino. *N Engl J Med 2006;355:1345-56.*

Neurologic Symptoms of TSC:
Subependymal Giant-Cell Tumours (SGCTs)

- SGCTs are well circumscribed, often calcified, slow-growing, low-grade tumours[1]
  - Larger and grow more rapidly than SENs
  - Some SGCTs may result in the development of hydrocephalus
- Intervention may be required because of a risk for permanent brain damage from tumor growth or hydrocephalus[2]:
  - Surgical removal, if feasible
  - Shunt implantation



A large SGCT along the midline of the brain near the foramen of Monro

1. Buccoliero. *Neuropathology* 2009;29:25-30.
2. Sharma. *Pathol Oncol Res* 2004;10:219-34.

TSC CANADA

Neurologic Symptoms of TSC:
Behavioral and Cognitive Impairments

Condition	Prevalence in TSC[1-4]
Autism Spectrum Disorder	17%-68%
Attention Deficit-Hyperactivity Disorder	>50%
Learning Disabilities	38%-80%
Mental Disabilities	40%-60%
Psychiatric Disorders	66%

1. Curatolo. *Child's Nerv Syst* 1996;12:515-21; 2. Kopp. *Epilepsy Behav* 2008;13:505-10;
3. Asato. *J Child Neurol* 2004;19:241-9; 4. Muzykewicz. *Epilepsy Behav* 2007;11:506-13.

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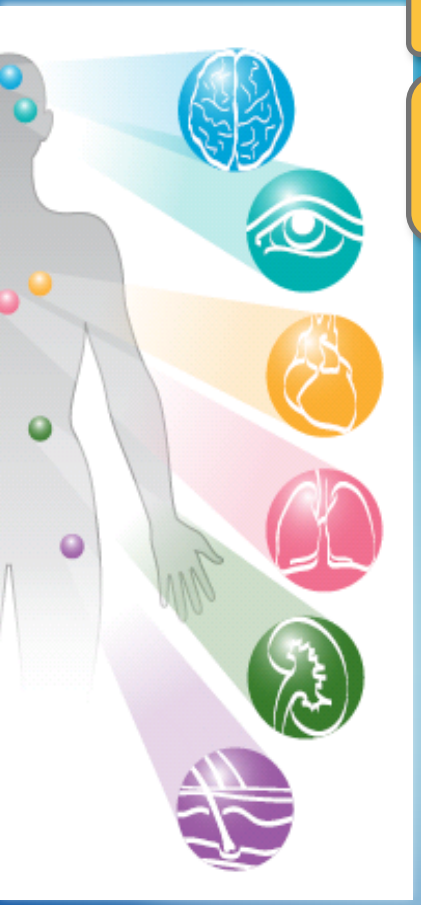

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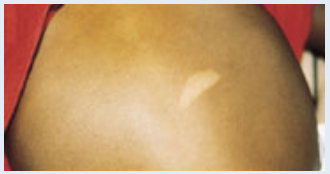
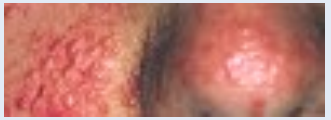
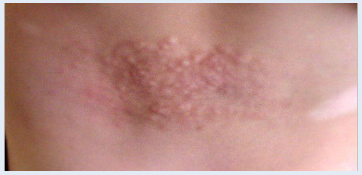
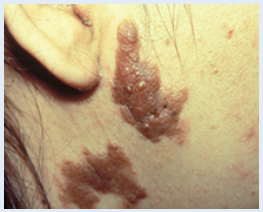
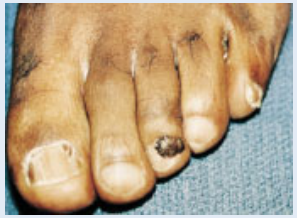
Dermatologic Symptoms of TSC[1,2]

Symptom	Prevalence	
Hypomelanotic macules	87-100%	
Facial Angiofibromas	70-80%	
Shagreen Patch	20-50%	
Fibrous Facial Plaques	Appx. 35%	
Ungual/Periungual fibromas	15-52%	

1. Leung. *J Ped Health Care.* 2007;21:108-14.
2. Bissler. www.tsalliance.org/pages.aspx?content=498. 2010.

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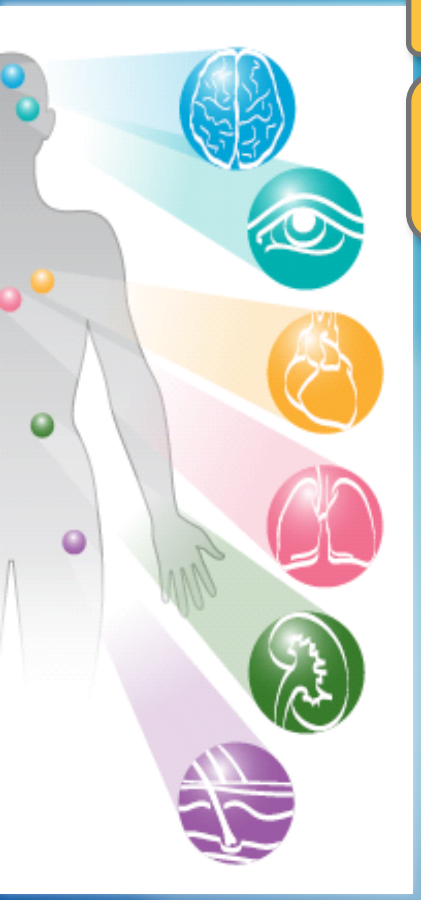

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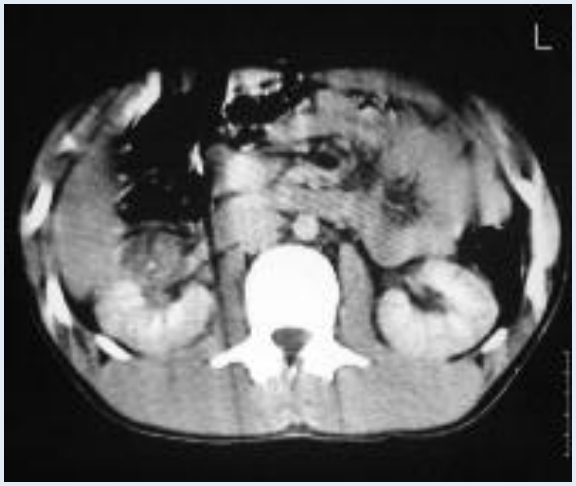
Renal Lesions – Angiomyolipomas (AML)

- Slow growing, bilateral kidney tumors[1,2]
- The following complications from AMLs may occur as a result of their mass effect[3,4]
  - Hemorrhage or rupture of blood vessels surrounding the tumor
  - Pain, nausea, vomiting, and hematuria
  - Destruction of adjacent renal tissue
  - Obstruction of urine flow
  - Risk for hypertension and renal failure
- Treatment may include arterial embolization and partial or complete removal of the kidney[4,5]



AML visible by MRI of the kidneys

1. Crino. *New Engl J Med* 2006;355:1345-56; 2. Bissler. www.tsalliance.org/pages.aspx?content=498;
3. Wintekorn et al. *Pediatr* Nephrol 2006;21:1189-93; 4.Umeoka. *RadioGraphics* 2008;10.1148/rg.e32;
5. Sooriakumaran. *BJU Int.* 2009;105:101-6.

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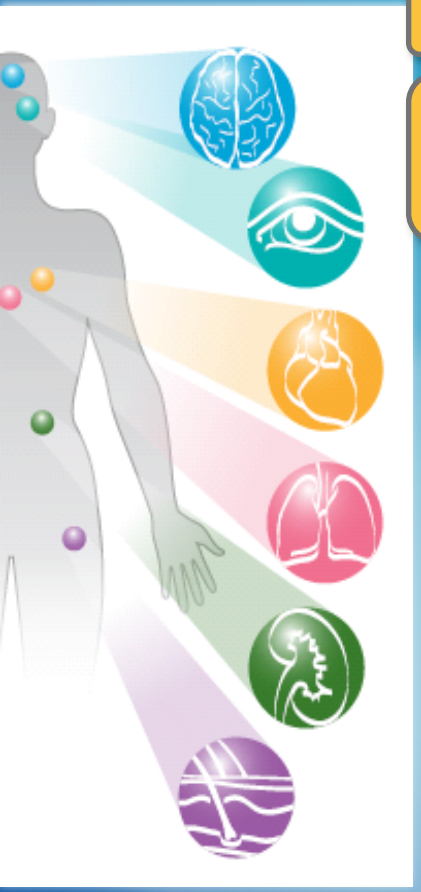

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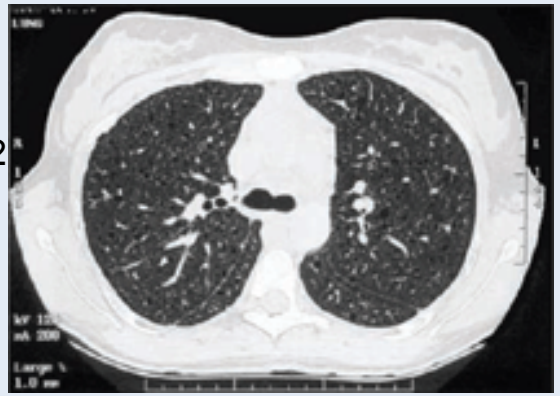
TSC Canada

Lung Feature – Lymphangioleiomyomatosis (LAM)

- Single or multiple cysts located in the lung[1,2]
- Occurs almost exclusively in women[1,2]
- The following complications from LAMs may occur[2]
  - Pneumothorax (collection of gases in space surrounding the lungs) due to cyst rupture
  - Pneumothorax may lead to difficulties in breathing (dyspnea) and coughing up blood (hemoptysis)
  - Multiple cystic lesions may lead to respiratory insufficiency and/or pulmonary hypertension (PTH)
- Treatment may include oxygen therapy, medication to lower PTH, surgery to prevent further pneumothorax, or lung transplant in extremely severe patients[2]



LAM visible by MRI of the lungs[3]

1. Moss. *Am J Respir Crit Care Med* 2001;164:669-71; 2. www.tsalliance.org/pages.aspx?content=4593;
3. Cahoon *Science* 2009; 323:204

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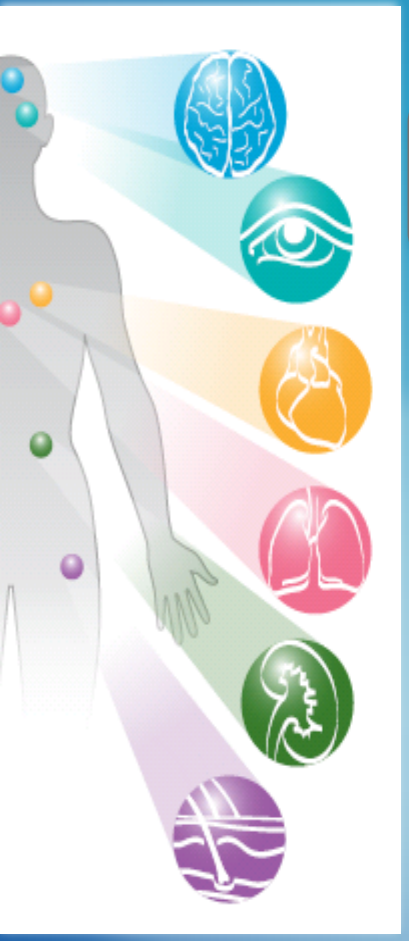

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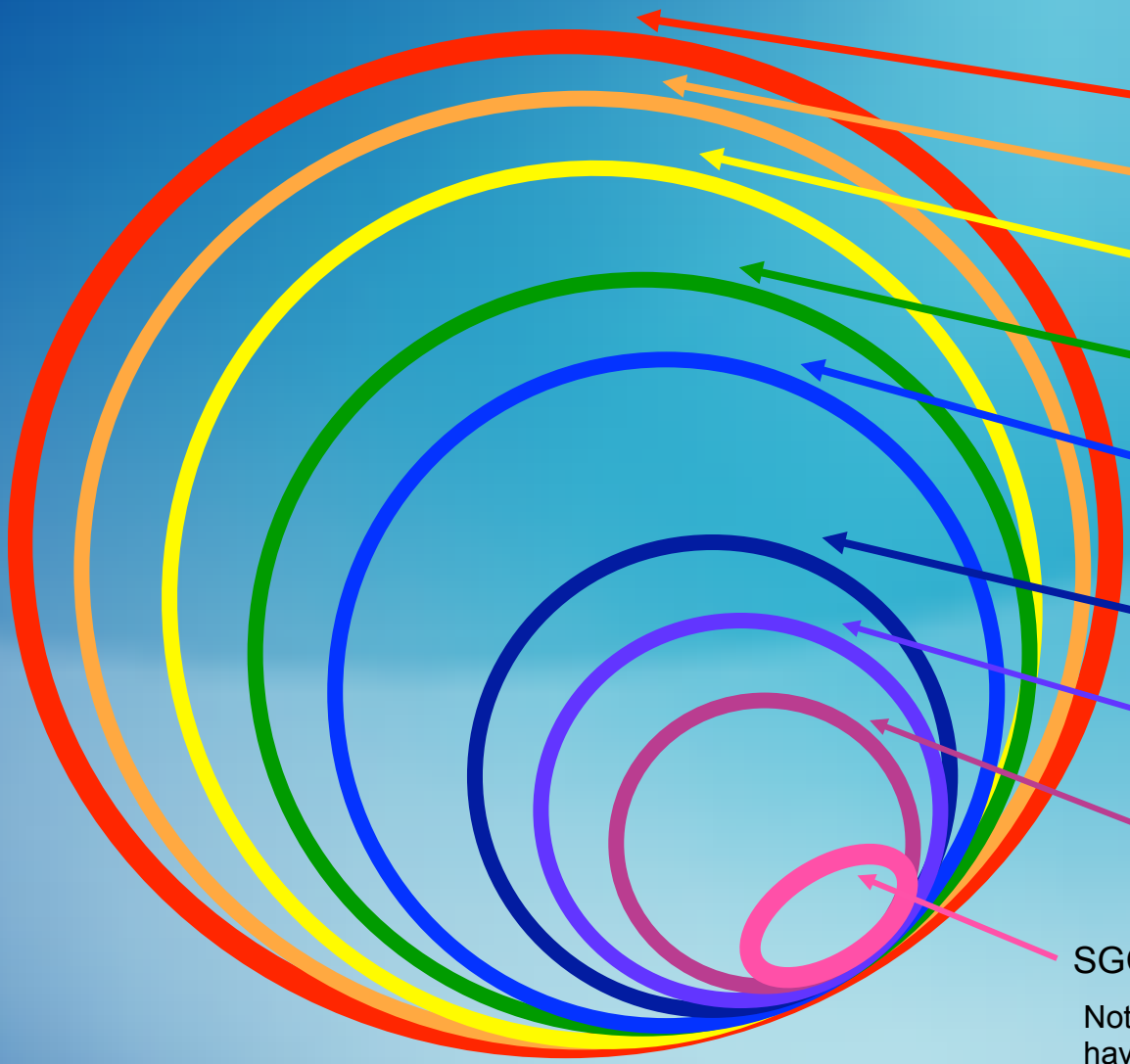
Frequency of Different Events in TSC



TSC 3,500+ Canada

90%-95% have seizures[1]

≈ 90% have cortical tubers[2]

60%-90% have subependymal nodules[3]

60%-80% have AMLs[4]

17%-61% are autistic

40% have infantile spasms

20%-25% have LAMs[5]

SGCT occur in 5%-15%6

Note: SGCT patients do not necessarily have all the other listed abnormalities

1. Yates. *Eur J Hum Genet.* 2006;14:1065-1073; 2. Crino. *Neurology.* 1999;53:1384-1390; 3. Christophe. *Brain Dev.* 2000;22:487-493; 4. Rakowski. *Kidney Intl*. 2006;70:1777-1782; 5. http://www.thelamfoundation.org/medical-providers/clinical-presentation-of-lam; 6. Shepherd. *Neurosurgery.* 1991;28:864-868.

TSC Canada

TSC Treatment Options

- Although the prognosis for many people living with Tuberous Sclerosis Complex is generally good, careful monitoring by specialists of all organ systems and overall development is critical
- Ultrasound *in utero* can detect heart tumors, assisting with early diagnosis and prompt monitoring in order to prevent complications related to TSC
- Treatment for people with TSC includes the management of seizures, special education for those who need it, and surgery
- The first medication for the treatment of SGCTs has recently been approved in Canada, for those patients for whom surgery is not a suitable option

TSC CANADA

TSC Research

- Tuberous Sclerosis Complex research is progressing rapidly, giving hope to affected families for more effective treatments
- With the increasing awareness of this disease, more research is being done on the causes and treatments for TSC patients
- Clinical trials of tumor-suppressing drugs continue to produce very encouraging results, with potential implications for treatment of multiple organ systems and hopefully even of some of the seizures and development delays caused by the disorder
- More than 15 clinical trials in TSC in the last 5 years appear on clinicaltrials.gov, investigating the causes/treatment of SGCTs, AMLs and LAMs, skin lesions, neurocognition, and autism

TSC CANADA

Canada's TSC Clinics

BC Children's Hospital, Vancouver, BC

- Director: Dr. Mary Connolly, Pediatric Neurologist
- Contact Nela Martic, Neurology Department, for more information
- Phone: (604) 875-2975
- Email: mconnolly@cw.bc.ca

Hôpital Ste-Justine, Montreal, QC

- Director: Dr. Philippe Major, Pediatric Neurologist
- Phone: (514) 345-4894
- For more information: www.chu-sainte-justine.org/STB

Clinic-building efforts continue in other cities in Canada.
For information and how to help, contact TSC Canada ST

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Français Sans Frais: 1-866-558-7278

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