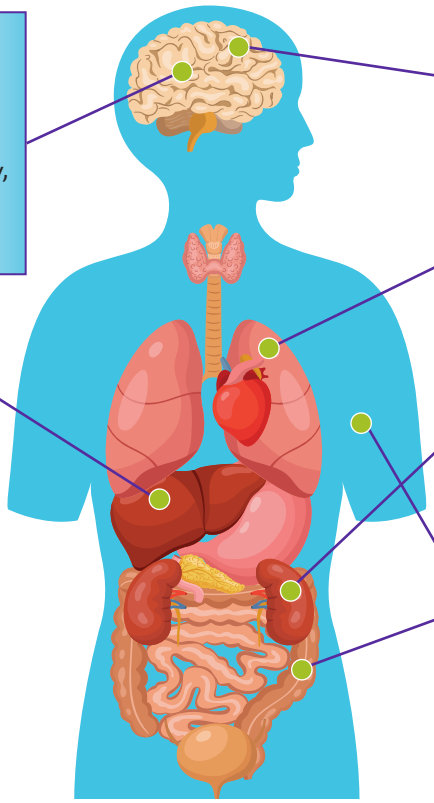
TSC Genes Lie at the Heart of a Network of Common Human Diseases

Neurology
Epilepsy, Infantile Spasms, Traumatic Brain Injury, Autism Spectrum Disorder, Aggression Disorders, Speech & Language Delay, Cognitive Impairment, Eating & Sleep Disorders, Communication Disorders, Anxiety, Depression, Attention Deficit Disorder, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease

Metabolic Diseases
Non-Alcoholic Fatty Liver Syndrome, Cardiovascular Disease, Type II Diabetes

Oncology
Malignant & Non-Malignant Brain Tumors, Megalocephaly, Skin Growths, Non-Malignant Heart Tumors, Irregular Pulmonary Growths, Retinal Lesions, Renal Cell Carcinoma



mTORopathies
Focal Cortical Dysplasia, Polyhydramnios, Megalencephaly, Symptomatic Epilepsy Syndrome & Hemimegalencephaly

Pulmonology
Lymphangioleiomyomatosis (LAM)

Nephrology
Renal Cysts, Polycystic Kidney Disorder, Angiomyolipomas

Autoimmune & Inflammation
Arthritis, Inflammatory Bowel Disease, Colitis, Crohn's Disease

The tuberous sclerosis complex (TSC) genes lie at the heart of a biochemical network that is disrupted in a diverse array of common human diseases and health concerns.

Research on TSC has revealed insights and therapeutic targets for numerous other diseases. The genetic mutations that give rise to TSC result in a loss of function in two key proteins: TSC1 and TSC2. These proteins are present in all human cells and function together to inhibit a growth-promoting protein called the mechanistic target of rapamycin or mTOR.

Chronic inhibition of TSC1 and TSC2, for example, is very common in cancer. These defects can also contribute to the development of autoimmune and inflammatory diseases. As a biochemical pathway regulated by insulin and nutrients, the TSC-mTOR pathway is also disrupted in common metabolic diseases, such as obesity and diabetes. Thus, TSC research provides critical insights into a diverse array of other diseases.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder that causes non-malignant tumors to form in vital organs including the brain, eyes, heart, kidneys, liver, skin, and lungs. TSC is caused by a mutation in either the TSC1 or TSC2 gene. Two-thirds of individuals with TSC have a sporadic genetic mutation, and one third inherit TSC from one of their parents. Individuals with TSC have a 50% chance of passing the condition on to each child.

In addition to multi-organ tumor growth, medical issues associated with TSC include varying degrees of neurological and behavioral issues. These medical problems not only vary between individual cases of TSC but are often complicated by the interdependent nature of behavior and neurology. As a result, the medical problems due to TSC may vary even between two family members (such as siblings) with TSC.

The incidence of TSC is estimated to be 1 in 6,000 live births. At least two children born each day in the United States will have TSC. Approximately 50,000 Americans and 1 million individuals worldwide have TSC, making TSC as common as ALS (Lou Gehrig's Disease) or Duchenne's Muscular Dystrophy.

The TSC Alliance improves quality of life for everyone affected by tuberous sclerosis complex (TSC) by catalyzing new treatments, driving research toward a cure and expanding access to lifelong support.

TSC and Epilepsy/Seizure Disorders

Seizures remain one of the most common neurological features of TSC, occurring in approximately 85% of individuals with TSC.

- Infants are often diagnosed with TSC after they begin having a very serious type of seizure called infantile spasms.
- Some children appear to develop normally until the onset of seizures, causing the loss of developmental milestones previously achieved.
- Older children and adults may develop multiple types of seizures including generalized, complex partial and other focal seizures.
- More than 50% of individuals with TSC who have epilepsy will not respond to standard antiepileptic medications, increasing the likelihood of intellectual impairment.

In addition to TSC-associated epilepsy, inconsistent control of mTOR is an underlying cause of the majority of familial epilepsies associated with focal cortical dysplasia, further demonstrating the importance of the TSC-mTOR pathway in epilepsy.

TSC and Autism Spectrum Disorders (ASD)

TSC leads to more cases of autism spectrum disorder (ASD) than any other single-gene disorder.

- An estimated 40-50% of individuals with TSC have ASD. The rate of ASD in the general population is substantially lower (approximately 1 in 59, or 1.7% of the total population).
- ASD is usually diagnosed in young children between the ages of 2 and 4 years. But in individuals with TSC, the diagnosis of ASD may go unrecognized due to other developmental disabilities.
- Physical abnormalities in brain development that occur in TSC are associated with impaired development of social communication skills.
- Recent animal studies indicate it may be possible to prevent or reverse intellectual disabilities and ASD if treated early.

Importantly, traits of ASD in TSC closely mimic ASD in the general population.

TSC and Cancer

Proteins produced by the TSC genes are key regulators of the mTOR pathway, an important biochemical network involved in the control of cell growth. Therefore, loss of function of these proteins in TSC is associated with uncontrolled growth leading to the development of widespread tumors.

The biochemical pathway affected by the TSC genes is also rendered dysfunctional in more than 50% of human cancers and underlies tumor development, progression and therapeutic resistance. The study of TSC is improving our understanding and revealing new treatment options in cancer.

Opportunities for Prevention of Epilepsy, Autism and Tumors

TSC is most frequently diagnosed in early childhood with the onset of seizures. However, heart tumors are often present in infants with TSC and are often detected by prenatal ultrasound, particularly in the third trimester. At birth, ash leaf-shaped spots on the skin are also a common feature of TSC. Increased recognition of these features has led to more frequent early diagnosis of TSC. Early diagnosis provides opportunities for timely interventions to prevent development of epilepsy, autism and other devastating childhood manifestations, as well as those occurring later in life, such as kidney tumors and LAM.

Biomarkers are needed to predict in advance those individuals with TSC at higher or lower risk of developing each manifestation. For instance, identification of an EEG biomarker before the onset of epilepsy in infants with TSC has led to a clinical trial to determine if a drug called vigabatrin can prevent the development and consequences of seizures.

Successful identification of additional biomarkers and preventative treatments for other features of TSC will undoubtedly spark research to determine if the same biomarkers are equally useful in the general population. This is yet another way in which research in TSC may provide a roadmap for the treatment and prevention of epilepsy, autism and cancer.

TSC Alliance

The TSC Alliance based in Silver Spring, Maryland is an internationally recognized nonprofit that does everything it takes to improve the lives of people with TSC. We drive research, improve quality care and access and advocate for all affected by the disease. The TSC community is our strongest ally. The collaboration of individuals and families, along with the partnership of other organizations, fuels our work to ensure people navigating TSC have support—and hope—every step of the way.

Together, we have raised awareness of TSC, accelerated discoveries that have led to new FDA-approved treatments and created support systems in the United States and around the world to improve TSC care and quality of life. Since 1984, the TSC Alliance has funded more than $37 million to further basic, translational and clinical research. But much more research is needed to identify new treatments and, one day, a cure.

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