TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM:

A Competitive, Peer-Reviewed Department of Defense Grant Program

"Our 3-year-old granddaughter, Emma, was diagnosed with TSC at age 2 months. Emma enrolled in the TSC-STEPS clinical trial within weeks of her diagnosis and started taking an mTOR inhibitor. TSC-STEPS builds on the groundbreaking work done through the CDMRP's TSC Research Program (TSCRP) linking TSC and the mTOR pathway. The study's goal is to see if seizures can be prevented using this class of drugs in addition to their demonstrated benefits of alleviating kidney, lung, and skin issues later in life. Controlling seizures has been fundamental to Emma's development. With them under control, she has changed from saying only a handful of words into a happy, talkative, and rambunctious 3-year-old who loves singing songs at preschool, riding her bike off of curbs, and hugging her baby sister. Imagine what lives could be like for future babies born with TSC if seizures could be prevented from ever happening. It has been a privilege to visit her from New Mexico regularly and see her grow and blossom. The TSCRP is vital to help Emma and others with TSC to reach their fullest potential."

DENNIS HILL, VETERAN USAF AND MARIANNE BAILEY HILL, VETERAN USAFR

FY2027 Request: Include at least $12 million in funding for the Tuberous Sclerosis Complex Research Program (TSCRP) at the Department of Defense (DoD).

For FY2026 the TSCRP had tremendous bipartisan support in the House (163 Dear Colleague Letter signers) and Senate (35 Dear Colleague Letter signers).

TSC Facts: Tuberous sclerosis complex (TSC) is a genetic disorder that can cause tumor growth in all of the body's vital organs. Symptoms commonly include seizures, kidney failure, brain and lung tumors, autism spectrum disorder, and severe learning disabilities. TSC occurs in approximately 1:6000 live births. Because two-thirds of TSC cases result from a spontaneous genetic mutation, TSC can affect any family. Critical cellular pathways disrupted in TSC are shared with other diseases, including cancer, lymphangioleiomyomatosis (LAM), and diabetes. Approximately 40% of women with TSC will develop LAM, and many more may develop cysts without knowing they may progress to LAM. LAM is a systemic neoplasm that results in cystic destruction of the lung. The TSC Alliance has funded more than $44 million to further basic, clinical, and translational research as part of this private/public partnership.

Military Value: The cellular pathways involved in TSC are also activated by traumatic brain injury, an all-too-common occurrence in military personnel.

- TSCRP-funded research has led to the development of mouse models used in research on both TSC and traumatic brain injury. Award W81XWH-12-1-0190, Wong, Michael. *The Role of Brain Inflammation in Epileptogenesis in TSC*
- Seizures often result from traumatic brain injury (TBI) in military personnel, and approximately 85% of individuals with TSC experience seizures during their lifetime.
- Award W81XWH-14-1-0061, is testing existing FDA-approved drugs for their ability to treat or prevent epilepsy by regulating the biochemical pathway shared between TSC and TBI. Raab-Graham, Kimberly. *Molecular Studies Investigating the Link Between Dendritic mRNA Translation and Repression Leading to Epilepsy in TSC*
- TSCRP-funded studies are also relevant to autism spectrum disorder, diabetes, cancer and other disorders that affect service personnel and their families.

Ensuring the health of military families improves the effectiveness of our fighting forces.

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

Competitive Awards with No Duplication of NIH Funding: All TSCRP grants are awarded on a competitive basis. An NIH program officer participates in the vision setting of TSCRP funding opportunities each year, and a DoD TSCRP officer participates in a trans-NIH meeting with program officers from all TSC-related NIH institutes. These practices ensure that TSCRP and NIH funds go to distinct, non-overlapping research projects.

More than Two Decades of Progress: Since its inception in FY2002, the TSCRP has supported research that is paving the way to cures and treatments for individuals with TSC and those with related disorders.

- **Hallmark achievement:** TSCRP-supported research that examined the role TSC genes play in cell growth and proliferation—specifically in controlling the mechanistic Target of Rapamycin (mTOR) signaling pathway in cells. This research rapidly led to clinical trials, resulting in the first drug approved by the FDA specifically for treatment of individuals with TSC.
- **Discovery of inflammation in the brain** in mice with mutations in TSC genes by an FY2011 award. This finding opens up potential new ways of treating TSC. Also, brain inflammation occurs in other disorders such as traumatic brain injury and Alzheimer's disease, enabling research impact to be shared among many disorders.
- **Effectiveness of a behavioral intervention strategy, JASPER, to improve outcomes in children with autism** is being tested in a large, NIH-funded clinical trial. This breakthrough trial would not be possible without data obtained from an FY2010 TSCRP clinical research award to define early autism predictors in TSC and an FY2014 TSCRP award for a pilot clinical trial.
- **Two TSCRP awards in FY2012 and FY2015** enabled generation of a potential approach for gene therapy of TSC, which has shown promising results in a mouse model of TSC tumors in the brain. Multiple companies are now working on TSC gene therapy because of the success of these early studies.
- **In 2022, the first rapamycin topical gel was FDA-approved** for treatment of facial angiofibromas in TSC. TSCRP funding in FY2010 funded a clinical trial of topical rapamycin which demonstrated effectiveness of this approach.
- **Two FY2023 awards address near-term needs of the TSC community,** one to understand the impact of caregiver wellbeing on behavioral and other neuropsychiatric issues in those with TSC for whom they are caring, and another to measure the risk and impact of lung and renal complications in women with TSC of child-bearing age and the impact of pregnancy. The occurrence of lung and kidney issues during pregnancy have been observed, but no quantitative data exists to guide healthcare at this critical point for mother and baby.
- **Creation of the first comprehensive natural history clinical database for TSC,** designed to understand how TSC progresses throughout a lifetime. To date 2,954 participants are enrolled at 24 sites. The database has helped recruit individuals for clinical trials and has been used to answer research questions.

None of this progress would have been possible without the financial support provided through the TSCRP, and quality research projects far outpace available funding.

FY2027 Summary: Funding for more innovative research is needed to prevent the manifestations of TSC and improve diagnosis and treatment of TSC and related diseases to reduce the healthcare burden imposed by this multi-organ disorder.

While this research has led to significant breakthroughs, far more funding is needed if we hope to find ways to more effectively treat those who suffer with TSC and prevent its occurrence in future generations. This increased funding is required to support clinical studies to validate biomarkers and outcome measurements necessary to accelerate development of new therapeutic agents, understand the biology underlying the wide variation in severity of manifestations among individuals with TSC, explore gene therapy, attract new researchers into this field of study, and develop assays and animal models necessary for translating basic scientific discoveries into clinical treatments.

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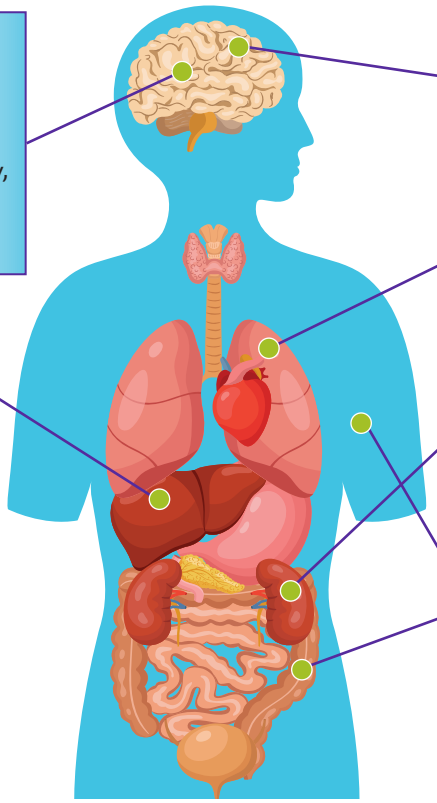
TSC Genes Lie at the Heart of a Network of Common Human Diseases

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 $44 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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About tuberous sclerosis complex

TSC causes tumors to grow in different organs and can impair their function, primarily the brain, heart, kidneys, skin and lungs.

TSC is the leading genetic cause of epilepsy.

UP TO 1 MILLION PEOPLE WORLDWIDE HAVE TSC.

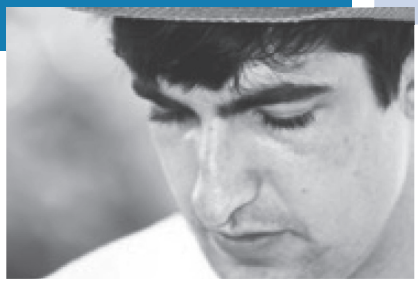
85%

OF PEOPLE WITH TSC EXPERIENCE SEIZURES, OF WHICH 2/3 HAVE MEDICATION-RESISTANT EPILEPSY.

TSC occurs in all races and ethnic groups and in both males and females.

About 1/3 of people with TSC inherit the disease, while the other 2/3 result from a spontaneous mutation.

Approximately **50,000** in the United States have TSC.



TSC affects an estimated **1 in 6,000** live births.

Autism occurs in about **50%** of people with TSC.

TSC impacts no two people in the same way – even identical twins.

Since 1984, the TSC Alliance has funded more than **$44 million** to further basic, translational and clinical research. But much more research is needed to identify new treatments and, one day, a cure.

Currently, there is no cure for TSC.

About the TSC Alliance

The TSC Alliance® is an internationally recognized nonprofit that does everything it takes to improve the lives of people with tuberous sclerosis complex (TSC). We improve quality of life for everyone affected by TSC by catalyzing new treatments, driving research toward a cure and expanding access to lifelong support.

TSC is a rare genetic disease that causes tumors to grow in different organs, from the brain and heart to the lungs and kidneys to the skin and eyes. Nearly one million people worldwide have TSC. Some live independently with few symptoms while others require complex care.

We are a source of hope and connection for all affected by TSC. We drive research, increase care quality and access and advocate with and for people affected by the disease. Through our collaboration and partnerships, we've advanced FDA-approved treatments and created support systems around the world so no one has to navigate TSC alone.

The TSC community is our strongest ally. With the power of families and the support of donors, volunteers, researchers, educators, industry partners and more, we can create a future where everyone with TSC can realize their full potential—no matter how complex their journeys are to get there. **Join us at tscalliance.org or contact us at info@tscalliance.org.**

What differentiates the TSC Alliance

The TSC Alliance is a model nonprofit in the rare disease research and support sector. Here are some ways we have demonstrated our unique ability to reach our constituents and impact their quality of life.

Facilitated 6,613
peer-to-peer connections in 2025, helping to reduce the stress and anxiety of a TSC diagnosis and provide ongoing support.

Established and built the first TSC Natural History Database, as well as a TSC Biosample Repository, and brought together a consortium of researchers who completed the first preventative clinical trial in both TSC and epilepsy.

800 million
media impressions in 2025 dramatically increasing the visibility of TSC.

Raised $22.6 million
from more than 1,800 engaged donors and community members since 2019 to accelerate research with the goal to change the course of TSC.

Galvanized the TSC community, and through their advocacy efforts, the Department of Defense Congressionally Directed Medical Research Program has appropriated

$131 million
toward TSC research since 2002.

Within our 14 Community Regions, **145** active leaders helped cultivate and mobilize more than **2,500** participants at volunteer-led, TSC community events.

Worked to support the FDA approval of **3 drugs** to treat TSC symptoms.

GreatNonprofits 2024 Top-Rated Nonprofit · Platinum Transparency 2024 Candid. · BBB Accredited Charity · Charity Navigator Four-Star

TUBEROUS SCLEROSIS COMPLEX RESEARCH PROGRAM

CDMRP
DEPARTMENT OF DEFENSE
CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

MISSION: Support innovative and high-impact research that promotes discoveries in TSC, from mechanistic insights to clinical application across all ages, by fostering new ideas and investigators to benefit Service Members, their Families and the public

Congressional Appropriations FY02-FY24:

$121M total

"The TSCRP plays a unique role in funding impactful TSC research. TSCRP's vision, mission and focus areas are reviewed and updated annually to ensure the program is funding the most relevant and timely research. Individuals living with TSC, or their family members, are involved in annual vision setting and in prioritizing applications for funding. Additionally, the TSCRP includes representatives from the NIH and TSC Alliance in these processes, ensuring the types of research funded by TSCRP are distinct from other organizations."

Steve Roberds, Ph.D.,
TSC Alliance,
FY23 Programmatic Panel Member

SCOPE OF THE PROBLEM

TSC is a *rare genetic disorder* caused by mutations in the TSC1 or TSC2 genes, causing tumor growth in multiple organs.

- Approximately **40,000–80,000** cases in the U.S.
- Up to **2 million** cases worldwide[1]

Affected organs may include:[2]

- **Brain**
- **Eyes**
- **Heart**
- **Lungs**
- **Kidneys**
- **Skin**

RELEVANCE TO MILITARY HEALTH

From 2013–2022, TSC-related MHS medical encounters for DOD Beneficiaries included:[3]

Average Patient Encounters	Outpatient Encounters	Hospital Bed Days
3,287	30,051	5,066

PROGRAM PRIORITIES

- Understanding, preventing, and treating the features of TSC-Associated Neuropsychiatric Disorders and reducing their impact
- Strategies for preventing and eradicating tumors and cysts associated with TSC
- Preventing epilepsy, improving treatment, and mitigating neurodevelopmental adverse outcomes associated with TSC-related seizures
- Developing, assessing, and testing emerging technologies to improve outcomes of TSC
- Understanding or improving outcomes of maternal-fetal health

[1] https://rarediseases.org/rare-diseases/tuberous-sclerosis/#affected
[2] https://www.ninds.nih.gov/health-information/disorders/tuberous-sclerosis-complex
[3] Defense Medical Surveillance System, The Armed Forces Health Surveillance Branch

For more information, visit: https://cdmrp.health.mil/tscrp

PROGRAM IMPACT AND OUTCOMES

The TSCRP invests in the full spectrum of product development.

RESEARCH BREAKTHROUGHS – MAKING A DIFFERENCE

Addressing Unmet Clinical Needs

- fMRI-guided brain surgery to reduce seizures
- Combined drug therapy: Imatinib and sirolimus
- Telehealth delivery of parent-child interaction therapy
- Novel biosensor for drug monitoring
- Behavioral intervention for TAND
- Language processing and epilepsy surgery
- TANDem2 – Longitudinal study of TAND

Developing Gene Therapies

- Gene replacement with AAV9 in TSC1 animal model
- Gene replacement with AAV9 in TSC2 animal model
- Extracellular vesicles as a platform to enhance TSC1 gene delivery

Improving Patient Care

- HYFTOR™ – FDA-approved topical medicine to treat facial angiofibroma
- JASPER – Behavioral intervention to improve social communication in children with TSC

KEY ACCOMPLISHMENTS BY THE NUMBERS

$194.4M follow-up funding

3 patent applications

4 patents

411 publications

66,191 citations

10 clinical trials

159 follow-up awards

1 FDA-approved drug: HYFTOR™

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