THE SMITH-KINGSMORE SYNDROME

Guide For Families and Medical Providers

WHAT IS SMITH-KINGSMORE SYNDROME?

Smith-Kingsmore syndrome (SKS) is a rare neurodevelopmental genetic disorder, identified in 2013, caused by changes (disease-causing variants) in the MTOR gene. The specific genetic change may vary for individuals with SKS, and therefore the symptoms may also vary. The most common features of SKS are:

- Intellectual Disability
- Developmental Disability
- Large Brain Size
- Seizures
- Sleep Disturbances

WHAT IS THE *MTOR* GENE?

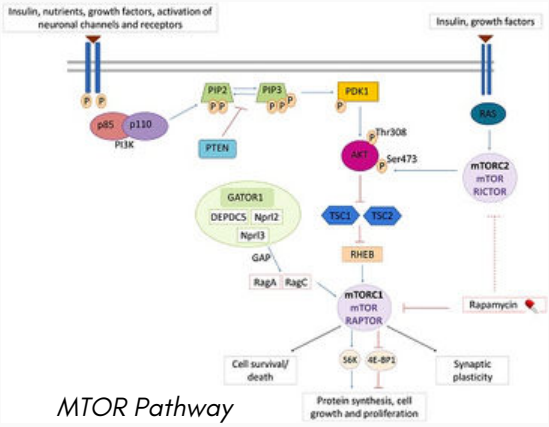
The instructions for our bodies are organized into structures called DNA. Genes are segments of DNA that give the instructions for a specific function or job.

The *MTOR* gene provides the body with instructions for the MTOR pathway. A pathway provides a way for cells of our body to communicate (like when to grow and how quickly to grow). The *MTOR* gene is located on Chromosome 1, specifically location 1p36.

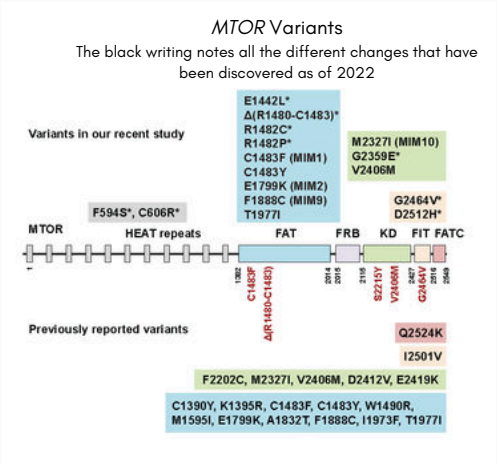
Changes (also called variants or mutations) in the *MTOR* gene can lead to hyperactivation (gain of function). As a result of pathway hyperactivation, the affected nerve cells (neurons) grow unusually large and misshapen, leading to brain malformations, cognitive delays and epilepsy.

Genetic changes within *MTOR* were first noted as a cause of a neurodevelopmental disorder in 2013. Studies are still needed to continue to define the characteristics associated with specific MTOR gene variants. Presently, genetic changes in MTOR can be separated into three clinical types.

- The first group includes patients with generalized brain overgrowth (megalencephaly), intellectual disability, autism, and hypotonia (what is commonly considered SKS).
- The second group includes patients with diffuse brain overgrowth, abnormalities of the surface of the brain (polymicrogyria), and skin pigmentation abnormalities.
- The third group includes patients with focal changes in the brain (focal cortical dysplasia or hemimegalencephaly) causing early-onset epilepsy.



MTOR Pathway



How did this happen?

All individuals have two copies of each gene, one inherited from each parent. SKS usually is an autosomal dominant condition, which means one copy of the altered *MTOR* gene in each cell is sufficient to cause the disorder.

Changes in the MTOR gene are usually random events (sporadic or de novo) that happen in the egg or sperm prior to conception and are not inherited from either parent. This type of change is present in all cells of the affected individual and is called a germline variant.

There are also some SKS patients who have an altered MTOR gene in some, but not all of their cells, and this is called somatic mosaicism. This type of change is also de novo (not inherited) and occurs at some point while a baby is developing during pregnancy. MTOR gene mutations in these SKS patients can only be detected in samples of affected tissues and might not be detected in a blood or saliva sample.

Rarely, people with SKS inherit the altered gene from an unaffected parent who has a MTOR gene mutation only in their sperm or egg cells (germline tissues). This is called germline mosaicism and, although rare, it has been seen more frequently in SKS than in other diseases.

What is the risk of this happening in future pregnancies?

The risk of a genetic change happening in more than one person in a family is called recurrence risk. Individuals with SKS have up to a 50% chance of having an affected child. However, it is difficult to calculate the exact risk because it depends on if the person with SKS has the change in every cell of their body or only in some cells.

How is someone diagnosed with SKS?

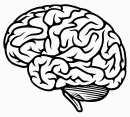
If a child has common features of SKS, genetic testing should be recommended. An SKS diagnosis is confirmed molecularly (genetic testing that looks for changes in the MTOR gene). The genetic testing is usually done with a blood or saliva sample.

If mosaicism (not all cells have a genetic change) is suspected, the genetic test may be performed on a different sample.

It is recommended that you talk with a genetics team to determine the type of test that would be best for your child.

Clinical Features or Manifestations

Common features of SKS vary. Explore here for a complete list.



Behavioral

- Autism/autistic traits/Sensory processing disorder
- ADHD (attention-deficit/hyperactivity disorder)
- Non-verbal / speech anomalies - delayed or absent speech, distorted articulation
- Self-harming behaviors

Neurologic

- Global developmental delays/Intellectual Impairment
- Macrocephaly / megalencephaly / Ventriculomegaly/Polymicrogyria/Other MRI Brain abnormalities/Rapid head growth first 6 months
- Low tone (hypotonia)
- Seizures (including nocturnal focal epilepsy)
- Sleep issues (insomnia, waking at night, sleep apnea)
- Hearing Impairment
- Cortical Visual Impairment

Physical

- Curly / wavy hair
- Abnormal facial features
  - frontal bossing, an open mouth appearance, a prominent and long philtrum, short nose with a flat nasal bridge, macrostomia, hypertelorism
- Macrosomia at birth (large for gestational age)
- Skin pigmentation/Blaschko lines/hypomelanosis of ito/hypermelanosis/Cafe au lait spots
- Decreased perspiration / heat intolerance
- Accelerated growth first 18 months to 2 years
- Delayed bone age (scan at 2 years were that of a newborn) / or slightly advanced bone age
- Motor skill deficits

Digestion/Gastrointestinal

- Digestive issues (abdominal pains, constipation)
- Hyperphagia - abnormally increased appetite for food

Is there a Cure or Treatment for SKS?

Currently, there is no cure for Smith-Kingsmore Syndrome, and no treatments approved by the U.S. Food and Drug Administration (FDA). Treatment is based on a child's specific symptoms.

Investigational Therapies

Some patients with SKS have been prescribed sirolimus (rapamycin) or everolimus to treat intractable seizures (seizures that cannot be controlled completely by other medications). There is currently no published data about how well this works (efficacy) and these drugs are not currently approved by the FDA to treat SKS. Studies are pending to determine the long-term effects of rapamycin on neurocognitive development in people with SKS and clinical trials are needed to clarify potential effectiveness of rapamycin.

Medical Concerns

Growth
Individuals with SKS are often large (macrosomia) at birth. Some are prenatally diagnosed with macrocephaly (large head), megalencephaly (large brain) and/or ventriculomegaly.

Muscle Tone
Individuals with SKS often have hypotonia (low muscle tone) which can result in delayed developmental milestones such as rolling over, sitting, crawling, walking.

Seizures
Approximately 30-40% of individuals with SKS have had a seizure. Many require anti-epileptic medications (AEDs) for ongoing management.

Sleep
Many families report sleeping problems with their SKS child. A sleep study can help identify issues and a sleep specialist or pediatrician may recommend medical management.

Hearing & Vision
There are reported cases of cortical visual impairment, where vision is impaired due to the way the brain processes what the eyes see. This may be due to abnormalities in the brain rather than abnormalities in the eyes. There are also reported cases of hearing loss due to damage to the inner ear or to the nerve pathways from the inner ear to the brain. There are a few individuals with SKS who have benefited from cochlear implants.

Gastrointestinal
Many individuals with SKS have gastrointestinal problems including constipation, motility issues, and gastroesophageal reflux. Approximately 30% of individuals have hyperphagia (abnormally increased appetite).

Developmental & Behavioral Concerns

Gross Motor:
Most individuals with SKS have delayed gross motor skills related to low muscle tone and benefit from early physical therapy. While most individuals with SKS can walk independently, there are some less than 8 years old who are working on this milestone and require mobility aids.

Fine Motor:
Individuals with SKS are often delayed in fine motor skills including pincer grasp, feeding oneself, and writing. These motor delays are related to low muscle tone.

Learning:
Learning difficulties vary from mild to severe. Children benefit from early childhood and interventional support. Some individuals are taught in mainstream school while others benefit from specialized instruction to meet their needs. The amount of support needed varies depending on the child's learning level and/or cognitive impairment. Continued support and supervision is usually necessary into adulthood.

Behavior:
Many individuals with SKS have been diagnosed with intellectual impairment and/or autism or have autism-like traits. There are documented cases of anxiety, ADHD, and OCD. While many individuals are friendly and happy, self-harm behaviors are common.

Speech:
Almost all individuals with SKS have delays in communication in both expressive and receptive language. Some are often late to start talking and may have a limited vocabulary while others remain nonverbal. Some individuals may benefit from alternative forms of communication including sign language, assistive technology devices, etc.

Management

Pediatrics:

- Annual visits to monitor growth and development
- Medical management of constipation is often needed
- Monitoring for illness due to abnormal immune cell function

Developmental Pediatrics:

- Developmental and behavioral evaluations to assess for challenges and to recommend treatments
- Evaluate for appropriate therapies including physical, occupational, speech/feeding, behavioral, vision therapy
- Guide individualized education plans (IEPs)

Genetics and Genetic Counseling:

- Review genetic testing and results
- Provide information about recurrence risk
- Provide coordination of care

Neurology:

- If seizures are suspected, an EEG (measurement of the brain's electrical activity) is recommended
- An MRI should be considered to identify any brain malformations

Ophthalmology/Neuro-ophthalmology:

- Screening for cortical visual impairment (CVI)

Audiology:

- Routine hearing screening (newborn and annually)

Endocrinology:

- Consider a referral if hypoglycemia develops or if premature (precocious) puberty is suspected

Orthopedics/Physical Rehabilitation:

- Evaluate the need for assistive devices due to hypotonia, motor deficits, and/or bone abnormalities

Neuropsychology:

- For school-age children, this assessment can help identify the most appropriate educational support and schooling

Routine dental and/or orthodontic care is also recommended as well as speech and language therapy, physical and occupational therapy and behavior therapy/psychological counseling.

Research

The CoRDS SKS Global Patient Registry is free for patients to enroll and contribute to future SKS research.
Additional research opportunities are updated on our website.

https://smithkingsmore.org/patient-registry/

Connect with us for support

The Smith-Kingsmore Syndrome Foundation is a 501 (c) (3) non profit organization dedicated to support the international SKS community. Our mission is to improve the quality of life for those impacted by SKS by supporting cutting-edge research and collaboration among medical professionals.
Connect with us on Socials: