# Smith-Kingsmore syndrome

## Description

Smith-Kingsmore syndrome is a neurological disorder characterized by a head that is larger than normal (macrocephaly), intellectual disability, and seizures. In some people with this condition, the ability to speak is delayed or never develops. Some children with Smith-Kingsmore syndrome have neurodevelopmental conditions known as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder, which is characterized by impaired communication and social interaction. Structural brain abnormalities may also be present in affected individuals. For example, one or both sides of the brain may be enlarged (hemimegalencephaly or megalencephaly) or have too many ridges on the surface (polymicrogyria), or the fluid-filled spaces near the center of the brain (ventricles) may be bigger than normal (ventriculomegaly).

Many people with Smith-Kingsmore syndrome have unusual facial features, such as a triangular face with a pointed chin, a protruding forehead (frontal bossing), widely spaced eyes (hypertelorism) with outside corners that point downward (downslanting palpebral fissures), a flat nasal bridge, or a long space between the nose and upper lip ( long philtrum). However, not everyone with Smith-Kingsmore syndrome has distinctive facial features.

## Frequency

Smith-Kingsmore syndrome is a rare condition with an unknown prevalence.

## Causes

Mutations in a gene called *MTOR* cause Smith-Kingsmore syndrome. The protein produced from this gene, called mTOR, is a key piece of two groups of proteins, known as mTOR complex 1 (mTORC1) and mTOR complex2 (mTORC2). These two complexes relay signals inside cells that regulate protein production and control several cellular processes, including growth, division, and survival. This mTOR signaling is especially important for growth and development of the brain, and it plays a role in a process called synaptic plasticity, which is the ability of the connections between nerve cells (synapses) to change and adapt over time in response to experience. Synaptic plasticity is critical for learning and memory.

*MTOR* gene mutations that cause Smith-Kingsmore syndrome increase the activity of

the mTOR protein and, consequently, mTOR signaling. As a result, protein production normally regulated by these complexes is uncontrolled, which impacts cell growth and division and other cellular processes. Too much mTOR signaling in brain cells disrupts brain growth and development and synaptic plasticity, leading to macrocephaly, intellectual disability, seizures, and other neurological problems in people with Smith-Kingsmore syndrome. Excessive mTOR signaling in other parts of the body likely underlies the unusual facial features and other less common signs and symptoms of the condition. It is unclear why the brain is particularly affected in people with Smith-Kingsmore syndrome.

Learn more about the gene associated with Smith-Kingsmore syndrome

- MTOR

## Inheritance

Smith-Kingsmore syndrome follows an autosomal dominant inheritance pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Most cases result from new (de novo) mutations in the gene that occur during the formation of reproductive cells (eggs or sperm) in an affected individual's parent or in early embryonic development. Rarely, people with Smith-Kingsmore syndrome inherit the altered gene from an unaffected parent who has an *MTOR* gene mutation only in their sperm or egg cells. This phenomenon is called germline mosaicism.

## Other Names for This Condition

- Macrocephaly, seizures, intellectual disability, umbilical hernia, and facial dysmorphism
- Macrocephaly-intellectual disability-neurodevelopmental disorder-small thorax syndrome
- MINDS syndrome
- SKS

## Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Macrocephaly-intellectual disability-neurodevelopmental disorder-small thorax syndrome (https://www.ncbi.nlm.nih.gov/gtr/conditions/C4225259/)

Genetic and Rare Diseases Information Center

- Macrocephaly-intellectual disability-neurodevelopmental disorder-small thorax

syndrome (https://rarediseases.info.nih.gov/diseases/13636/index)

Patient Support and Advocacy Resources

- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Clinical Trials

- ClinicalTrials.gov (https://clinicaltrials.gov/search?cond=%22Smith-Kingsmore syndrome%22)

Catalog of Genes and Diseases from OMIM

- SMITH-KINGSMORE SYNDROME; SKS (https://omim.org/entry/616638)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Smith-Kingsmore%29+OR+%28%28MTOR%5BTI%5D%29+AND+%28megalencephaly%5BTI%5D%29%29+OR+%28%28MTOR%5BTI%5D%29+AND+%28intellectual+disability%5BTI%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D)

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