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PLAIN LANGUAGE SUMMARY

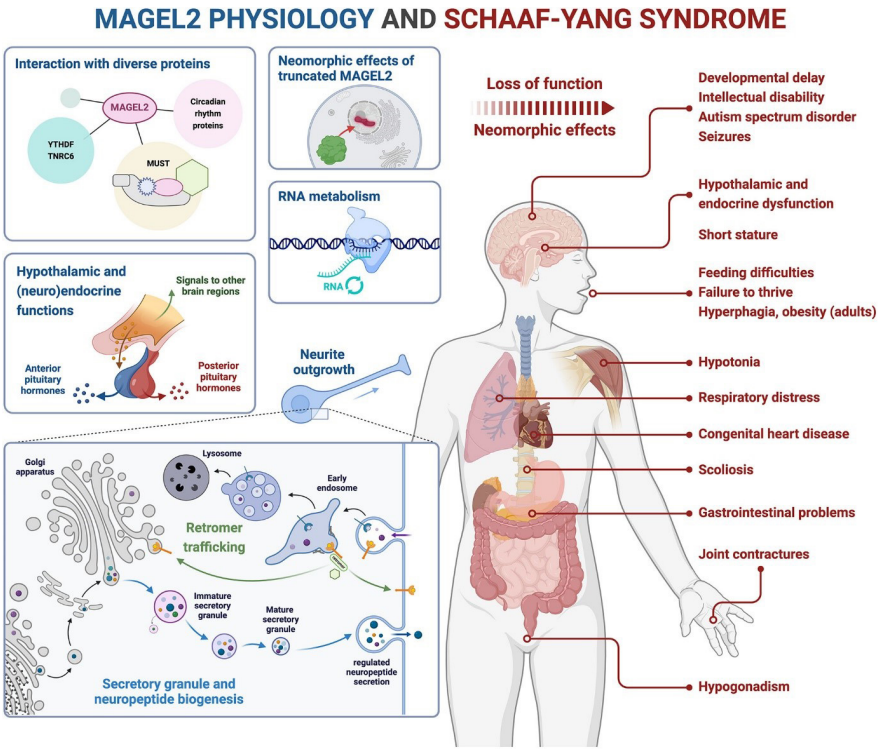
MAGEL2 (patho)physiology and Schaaf–Yang syndrome

Schaaf–Yang syndrome (SYS) is a complex disorder affecting brain development and function. Individuals living with SYS often take longer to learn skills like walking, have intellectual challenges, show signs of autism, and frequently experience joint problems. Many symptoms are related to dysfunction of the hypothalamus, a brain region that regulates essential body functions like hormones, temperature, hunger, and sleep. SYS is caused by genetic variants in the gene *MAGEL2*. There is some similarity to Prader–Willi syndrome because *MAGEL2* is one of many genes also involved in that syndrome.

Currently, there is no cure for SYS. Available treatments focus on managing symptoms rather than addressing the underlying cause. Common therapies include speech and physical therapy, psychiatric treatment, and hormone replacement. Growth hormone treatments particularly have shown promise, improving height, body mass index, muscle strength, and social skills in some patients. Oxytocin (which acts on internal body organs and as a chemical messenger in the brain) therapy shows promise in animal studies by improving social skills, learning, memory, and eating behavior. Oxytocin therapy for disorders similar to SYS have yielded mixed results. Oxytocin may work best during specific developmental periods and in combination with behavioral therapy but this must be confirmed with clinical trials.

MAGEL2 mostly acts during brain development and in the hypothalamus. In most cases of SYS, the gene is changed such that a shorter, defective MAGEL2 protein is produced. This defective protein cannot function properly. In addition, it is likely that the defective protein has harmful effects beyond that. Therefore, a potential therapeutic approach could reduce the levels of the defective protein with compounds like antisense oligonucleotides (small pieces of DNA or RNA that can bind to specific molecules of RNA), which reduce defective protein levels indirectly, or proteolysis targeting chimeras (small, readily designed molecules), which directly act on the defective protein.

The review summarized here contains the current scientific knowledge on the SYS gene *MAGEL2*, providing individuals with lived experience and researchers with the most up-to-date information. We hope this will guide and spark therapeutic advancements for SYS.



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