KARS gene

The KARS gene, also known as the KARS1 gene, encodes lysyl-tRNA synthetase (KARS), an enzyme crucial for protein synthesis. KARS is responsible for attaching lysine to its corresponding tRNA, a process essential for the translation of mRNA into protein. Mutations in the KARS gene can lead to various clinical manifestations, often associated with mitochondrial diseases, given the enzyme's role in cellular energy production.

Clinical Implications of KARS Mutations Neurological Disorders:

Charcot-Marie-Tooth Disease: Some mutations in KARS are linked to Charcot-Marie-Tooth disease, a group of inherited disorders affecting the peripheral nerves. Symptoms include muscle weakness and atrophy, particularly in the feet and legs, and may extend to the hands and arms. Epileptic Encephalopathy: KARS mutations can lead to early-onset epileptic encephalopathy, characterized by severe, treatment-resistant seizures and significant developmental delays. Hearing Loss:

Mutations in KARS have been associated with nonsyndromic hearing loss. This is a form of hearing impairment not associated with other signs and symptoms. Mitochondrial Dysfunction:

Given the role of KARS in mitochondrial function, mutations can lead to broader mitochondrial disorders, which may manifest as muscle weakness, neurological issues, and other systemic symptoms. Molecular and Functional Impact Protein Synthesis Impairment: Mutations in KARS can directly impair the enzyme's ability to charge tRNA with lysine, disrupting protein synthesis. Mitochondrial Dysfunction: As KARS is also involved in mitochondrial translation, mutations can lead to mitochondrial dysfunction, contributing to a range of systemic and neurological symptoms. Diagnosis and Research Genetic Testing: Identifying mutations in the KARS gene typically involves next-generation sequencing techniques, which can pinpoint specific mutations associated with clinical symptoms. Functional Studies: Research often focuses on understanding how specific mutations affect KARS enzyme activity and mitochondrial function. This includes biochemical assays and studies in model organisms. Management and Treatment Currently, there is no specific cure for conditions caused by KARS mutations. Management typically involves symptomatic treatment and supportive care:

Neurological Symptoms: Antiepileptic drugs may be used for seizure management, and physical therapy can help manage muscle weakness. Hearing Loss: Hearing aids or cochlear implants may be beneficial for those with hearing impairment. Conclusion KARS mutations can lead to a range of clinical manifestations, primarily affecting the nervous system and hearing. Ongoing research aims to better understand the molecular mechanisms underlying these conditions, which is crucial for developing targeted therapies in the future.

Yu et al. reported for the first time that pathogenic variants p.R477H and p.P505S in KARS, which encodes lysyl-tRNA synthetase (LysRS), cause leukoencephalopathy with progressive cognitive impairment in humans. The role and action mechanisms of KARS in brain myelination during development are unknown. Here, we first generated Kars knock-in mouse models through the CRISPR-Cas9 system. Kars knock-in mice displayed significant cognitive deficits. These mice also showed significantly reduced myelin density and content, as well as significantly decreased myelin thickness during development. In addition, Kars mutations significantly induced oligodendrocyte differentiation arrest and reduction in the brain white matter of mice. Mechanically, oligodendrocytes' significantly

imbalanced expression of differentiation regulators and increased capase-3-mediated apoptosis were observed in the brain white matter of Kars knock-in mice. Furthermore, Kars mutations significantly reduced the aminoacylation and steady-state level of mitochondrial tRNALys and decreased the protein expression of subunits of oxidative phosphorylation complexes in the brain white matter. Kars knock-in mice showed decreased activity of complex IV and significantly reduced ATP production and increased reactive oxygen species in the brain white matter. Significantly increased percentages of abnormal mitochondria and mitochondrion area were observed in the oligodendrocytes of Kars knock-in mouse brain. Finally, melatonin (a mitochondrion protectant) significantly attenuated mitochondrion and oligodendrocyte deficiency in the brain white matter of KarsR504H/P532S mice. The mice treated with melatonin also showed significantly restored myelination and cognitive function. Our study first establishes Kars knock-in mammal models of leukoencephalopathy and cognitive impairment and indicates important roles of KARS in the regulation of mitochondria, oligodendrocyte differentiation and survival, and myelination during brain development and application prospects of melatonin in KARS (or even aaRS)-related diseases [1)].

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Yu L, Chen Z, Zhou X, Teng F, Bai QR, Li L, Li Y, Liu Y, Zeng Q, Wang Y, Wang M, Xu Y, Tang X, Wang X. KARS Mutations Impair Brain Myelination by Inducing Oligodendrocyte Deficiency: One Potential Mechanism and Improvement by Melatonin. J Pineal Res. 2024 Aug;76(5):e12998. doi: 10.1111/jpi.12998. PMID: 39087379.