FULL-LENGTH ARTICLE NPub.org/jc2lcv

Biallelic variants in *LARS2* and *KARS* cause deafness and (ovario)leukodystrophy

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Study objective and summary result

This study explored the leukodystrophy syndromes resulting from pathogenetic variants of the *LARS2* and *KARS* genes, and it found that these gene variants can cause syndromes involving deafness, ovarian failure, and leukodystrophy with a mitochondrial signature.

What is known and what this paper adds

Mutations in *-ARS* and *-ARS2* genes are a documented cause of leukodystrophy syndromes. This study characterizes additional leukodystrophy syndromes resulting from mutations in *LARS2* and *KARS*.

Participants and setting

This study examined 5 patients with leukodystrophy syndromes. Patient 1 was identified through the Amsterdam Database of Unclassified Leukodystrophies. Patients 2–5 were identified based on diagnostic whole-exome sequencing results. These patients were selected based on the presence of pathogenetic mutations in *LARS2* and *KARS*. Patients 1 and 4 were women, and patients 2, 3, and 5 were men.

Design, size, and duration

This study conducted whole-genome sequencing on genomic DNA from patient 1 and whole-exome sequencing on DNA samples from patients 2–5. This study collected clinical information, including brain MRI images for all patients; magnetic resonance spectroscopy (MRS) findings for patients 1, 2, and 5; and brain autopsy findings for patient 1. The study also included assessment of aminoacylation activities of purified mutant recombinant mitochondrial leucyl tRNA synthase and aminoacylation assays on patients' lymphoblasts and fibroblasts.

Primary outcome measures

The primary outcomes were the clinical features of the patients' leukodystrophy syndromes.

Main results and the role of chance

Patients 1–4 carried *LARS2* mutations, and patient 5 carried *KARS* mutations. The patients had early-onset deafness. They also experienced neurologic deterioration, and their MRIs revealed progressive white matter abnormalities. The female patients experienced premature ovarian failure. MRS in patients 1 and 5 revealed elevated white matter lactate levels, which suggested mitochondrial disease. This study mentions *LARS2* and *KARS* pathogenic variants as gene defects that may underlie deafness, ovarian failure and leukodystrophy with mitochondrial signature. We discussed the specific MRI characteristics shared by leukodystrophies caused by mitochondrial tRNA synthase defects and proposed adding aminoacylation assays as biochemical diagnostic tools for leukodystrophies.

Table Kinetic measures for leucylation of *E. coli* tRNALeu(UAA) transcript by wild-type (WT) and variant recombinant mtLeuRS

LARS2 variant	Km (μM)	kcat (min^{-1})	kcat/Km (min^{-1} μM^{-1} 10^{-3})
WT	0.60	12.0	20.0
p.N124I	0.65	4.2	6.5
p.R663W	0.54	4.0	7.4

Bias, confounding, and other reasons for caution

This study did not have a consistent set of full assessment data for all patients.

Generalizability to other populations

The inclusion of only 5 patients may limit the generalizability of this study's results.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.