

# Scientists reveal the genetic basis of mitochondrial diseases

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Mutations in genes encoding mitochondrial aminoacyl-tRNA synthetases are linked to diverse diseases. However, the precise mechanisms by which these mutations affect mitochondrial function and disease development are not fully understood.

A joint team led by Dr. Ge Wanzhong from the Women's Hospital,

Zhejiang University School of Medicine, and Prof. Guan Min-Xin from the Institute of Genetics, Zhejiang University, published their collaborative research regarding the developmental delay and seizure manifested by aberrant mitochondrial tRNA metabolism in the journal *Nucleic Acids Research* on December 8.

In this study, the research team focused on FARS2 deficiency and illustrated how the aberrant mitochondrial tRNA metabolism can lead to developmental delay and seizure, two major clinical phenotypes associated with FARS2 [mutations](#).

The researchers generated *Drosophila* FARS2 knockout and knockdown models and performed a series of experiments to confirm the validity of the model for studying mitochondrial tRNA synthetases-related diseases. They found that FARS2 deficiency caused defects in mitochondrial tRNA<sup>Phe</sup> metabolism, translation, assembly and activity of oxidative phosphorylation system (OXPHOS) complexes. Moreover, the developmental delay and seizure observed in *Drosophila* FARS2 deficiency model accurately recapitulated many phenotypic features of human disease.

The team also produced humanized fly models by introducing human wild type FARS2, p.G309S and p.D142Y pathogenic variants into *Drosophila* FARS2 mutants, and analyzed the pathologic consequences of human disease-causing FARS2 p.G309S and p.D142Y mutations. These new findings suggest that proper control of mitochondrial tRNA [metabolism](#) is essential for mitochondrial function, revealing a novel genetic basis for mitochondrial [disease](#).

"Our research discoveries will facilitate new understanding of pathogenesis of mitochondrial diseases and new therapies for treating seizures," said Ge.

**More information:** Wenlu Fan et al, FARS2 deficiency in *Drosophila* reveals the developmental delay and seizure manifested by aberrant mitochondrial tRNA metabolism, *Nucleic Acids Research* (2021). [DOI: 10.1093/nar/gkab1187](https://doi.org/10.1093/nar/gkab1187)

Provided by Zhejiang University

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