AIF3 splicing variant elicits mitochondrial malfunction and neurodegeneration via the concurrent dysregulation of electron transport chain and glutathione-redox homeostasis

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Genetic mutations in apoptosis-inducing factor (AIF) have a strong association with mitochondrial disorders; however, little is known about the aberrant splicing variants in affected patients and how these variants contribute to mitochondrial dysfunction, brain development defects and/or neurodegeneration. We identified pathologic AIF3/AIF3-like splicing variants in postmortem brain tissues of pediatric individuals with mitochondrial disorders. Mutations in AIFM1 exon-2/3 increase splicing risks. AIF3-splicing disrupts mitochondrial complexes, membrane potential, and respiration, causing brain development defects and neurodegeneration in aging-related diseases. Mechanistically, AIF is a mammalian NAD(P)H dehydrogenase and possesses glutathione reductase activity controlling respiratory chain functions and glutathione regeneration. Conversely, AIF3, lacking these activities, disassembles mitochondrial complexes, increases ROS generation, and simultaneously hinders antioxidant defense. Expression of NADH dehydrogenase NDI1 restores mitochondrial functions partially and protects neurons in AIF3-splicing mice. Our findings unveil an underrated role of AIF as a mammalian mitochondrial complex-I alternative NAD(P)H dehydrogenase and provide insights into pathologic AIF-variants in mitochondrial disorders and related neurological diseases.

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