
AMPD2 regulates GTP synthesis and is mutated in a potentially treatable neurodegenerative brainstem disorder.

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Authors: Naiara Akizu, Vincent Cantagrel, Jana Schroth, Na Cai, Keith Vaux, Douglas McCloskey, Robert K Naviaux, Jeremy Van Vleet, Ali G Fenstermaker, Jennifer L Silhavy, Judith S Scheliga, Keiko Toyama, Hiroko Morisaki, Fatma M Sonmez, Figen Celep, Azza Oraby, Maha S Zaki, Raidah Al-Baradie, Eissa A Faqeih, Mohammed A M Saleh, Emily Spencer, Rasim Ozgur Rosti, Eric Scott, Elizabeth Nickerson, Stacey Gabriel, Takayuki Morisaki, Edward W Holmes, Joseph G Gleeson

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Public Summary:

Purine biosynthesis and metabolism, conserved in all living organisms, is essential for cellular energy homeostasis and nucleic acid synthesis. The de novo synthesis of purine precursors is under tight negative feedback regulation mediated by adenosine and guanine nucleotides. We describe a distinct early-onset neurodegenerative condition resulting from mutations in the adenosine monophosphate deaminase 2 gene (AMPD2). Patients have characteristic brain imaging features of pontocerebellar hypoplasia (PCH) due to loss of brainstem and cerebellar parenchyma. We found that AMPD2 plays an evolutionary conserved role in the maintenance of cellular guanine nucleotide pools by regulating the feedback inhibition of adenosine derivatives on de novo purine synthesis. AMPD2 deficiency results in defective GTP-dependent initiation of protein translation, which can be rescued by administration of purine precursors. These data suggest AMPD2-related PCH as a potentially treatable early-onset neurodegenerative disease.

Scientific Abstract:

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