24. MISCELLANEOUS / NEW DISEASE GROUP : Oral / Poster

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Aminoacyl-tRNA synthetase deficiencies: in search of common themes

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BACKGROUND:
By attaching amino acids to their cognate tRNAs, aminoacyl-tRNA synthetases (ARSs) play an important role in protein translation. Mutations in genes encoding these enzymes are increasingly associated with human disease. Clinical features of autosomal recessive ARS deficiencies appear very diverse and without apparent logic.

METHODS:
We searched for all patients with recessive ARS mutations in literature (July 2017). Clinical and laboratory findings of all patients were categorized. Additionally, we deep-phenotyped five patients with novel IARS, KARS, LARS and QARS mutations seen in our own hospital. We considered symptoms to be common if they occurred in > 30% of individual ARS deficiencies.

RESULTS:
We identified 107 patients with homozygous or compound heterozygous mutations in the cytosolic genes AARS, DARS, HARS, IARS, LARS, MARS, RARS, SARS, VARS and YARS, and the combined cytosolic and mitochondrial genes GARS, KARS and QARS. All presented with abnormalities of the central nervous system and/or senses, and nearly all with failure to thrive. Other common symptoms included feeding problems, dysmaturity, liver symptoms, and various endocrine abnormalities. All 3 combined mitochondrial and cytosolic and several cytosolic ARS deficiencies showed signs of mitochondrial dysfunction and facial dysmorphisms. Symptoms were most severe in the first year of life and during infections. Deep-phenotyping of our five patients revealed anemia, interstitial lung disease and renal tubulopathy as additional common symptoms.

DISCUSSION:
Deep-phenotyping of reported and new patients with recessive ARS deficiencies enabled us to discern a common clinical phenotype, putatively resulting from insufficient aminoacylation activity to meet translational demand in specific organs or periods of life. Assuming residual ARS activity, adequate protein/amino acid supply seems essential instead of the traditional replacement of protein by glucose in patients with metabolic diseases.

Previously Presented?

Previously presented in a publication A paper was very recently accepted for publication in Genetics in Medicine.

Conflict of Interest

NONE