Abstract


NAD Deficiency, Congenital Malformations, and Niacin Supplementation.


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BACKGROUND: Congenital malformations can be manifested as combinations of phenotypes that co-occur more often than expected by chance. In many such cases, it has proved difficult to identify a genetic cause. We sought the genetic cause of cardiac, vertebral, and renal defects, among others, in unrelated patients.

METHODS: We used genomic sequencing to identify potentially pathogenic gene variants in families in which a person had multiple congenital malformations. We tested the function of the variant by using assays of in vitro enzyme activity and by quantifying metabolites in patient plasma. We engineered mouse models with similar variants using the CRISPR (clustered regularly interspaced short palindromic repeats)-Cas9 system.

RESULTS: Variants were identified in two genes that encode enzymes of the kynurenine pathway, 3-hydroxyanthranilic acid 3,4-dioxygenase (HAAO) and kynureninase (KYNU). Three patients carried homozygous variants predicting loss-of-function changes in the HAAO or KYNU proteins (HAAO p.D162*, HAAO p.W186*, or KYNU p.V57Efs*21). Another patient carried heterozygous KYNU variants (p.Y156* and p.F349Kfs*4). The mutant enzymes had greatly reduced activity in vitro. Nicotinamide adenine dinucleotide (NAD) is synthesized de novo from tryptophan through the kynurenine pathway. The patients had reduced levels of circulating NAD. Defects similar to those in the patients developed in the embryos of Haao-null or Kynu-null mice owing to NAD deficiency. In null mice, the prevention of NAD deficiency during gestation averted defects.

CONCLUSIONS: Disruption of NAD synthesis caused a deficiency of NAD and congenital malformations in humans and mice. Niacin supplementation during gestation prevented the malformations in mice.

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