A De Novo Missense Variant In The DEAD-box Gene EIF4A1 Detected In Two Children With Congenital Malformations And Developmental Delay

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DEAD-box proteins are a subset of RNA helicases that contain multiple conserved motifs, including one with the amino acid sequence Aspartic acid-Glutamic acid-Alanine-Aspartic acid (or “D-E-A-D” in single letter abbreviations). Their functions include a variety of intracellular roles, including translation initiation, RNA metabolism, and others. Eukaryotic initiation factor 4A, isoform 1 (EIF4A1) is a DEAD-box gene also known as DDX2A. Its protein product is part of the translation initiation complex and was one of the earliest RNA helicases characterized, with known effects in translation of oncogenes. Gene variants in EIF4A1 have not been reported previously to cause congenital anomaly syndromes. Pathogenic variants in other RNA helicase genes, such as DDX3X, DHX30, and EIF4A3 have been associated with neurodevelopmental disorders that can include visceral malformations. We report two children with congenital heart defects, other malformations, feeding problems, and developmental delay who have the same variant in the EIF4A1 gene. The heterozygous, de novo missense change, c.1019G>A, is found in the conserved helicase C-terminal domain.