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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Introduction

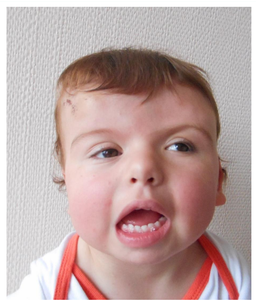
Eukaryotic initiation factor 4A1 (*EIF4A1*) is a DEAD-box gene also known as *DDX2A* and is located at 17p13.1. Its protein product is part of the translation initiation complex and was one of the earliest RNA helicases characterized, with known effects in translation of oncogenes. Gene variants in *EIF4A1* have not been reported previously to cause congenital anomaly syndromes. We report two unrelated children with congenital heart defects, other malformations, feeding problems, and developmental delay who have the same variant in the *EIF4A1* gene.

Clinical History

In both cases, complex congenital heart disease was diagnosed by prenatal ultrasound. Patient 1 also had congenital diaphragmatic hernia detected prenatally. Both patients had normal chromosome analysis, microarray analysis, a targeted gene panel, and eventually whole exome sequencing (WES). Through GeneMatcher, the two cases were recognized to have similar phenotypes with the same *de novo* variant. Clinical findings are summarized in the table. Pertinent negative findings in both cases include: normal head circumference, no regression, no behavioral issues, and no seizures.

Patient 1 at 15 months of age

Patient 2 at 1 month of age (left), 21 months (right), and 4 years 5 months (below)



Acknowledgement

We sincerely thank the patients and their families for sharing their information and photographs.

Clinical Findings

	Patient 1 (USA)	Patient 2 (France)
Weight	-2.0 SD at 15 months	-5 SD at 21 months -1.9 SD at 4 years
Height	-3.7 SD at 15 months	Normal
Cranium	Plagiocephaly, broad forehead	Craniosynostosis of left coronal suture; surgery at 17 months
Face	Round, broad	Asymmetry, full cheeks
Eyes	Hypertelorism, telecanthus	Strabismus, hyperopia, epicanthic folds
Ears	Normal	Mild posteriorly rotated ears Normal hearing
Nose	Low nasal bridge	Bulbous
Mouth	Mildly thickened gums	(Not described)
Neck	Short	(Not described)
Chest	Diaphragmatic hernia	Inverted nipples
Hands	Normal	Left single palmar crease
Respiratory Status	Chronic respiratory failure; tracheostomy and ventilator dependent; pulmonary hypoplasia; bronchomalacia	Nocturnal oxygen until 7 months of age Asthma
Cardiac Status	Tetralogy of Fallot Pulmonary hypertension	Patent ductus arteriosus, ventricular septal defect, atrial septal defect Pulmonary hypertension
Digestive Status	Dysphagia Nissen, gastrostomy Gastroesophageal reflux	Feeding/orality troubles Nissen, gastrostomy (still required at age 4) Some vomiting until age 3
Genitalia	Small scrotum	(Not described)
Neurological	Normal deep tendon reflexes	Brisk patellar reflexes, no Achilles reflexes
Cranial imaging (MRI)	Bilateral subcortical white matter hyperintensity Enlarged cerebrospinal fluid spaces and ventricles, likely volume loss.	Mild periventricular and subcortical white matter hyperintensity
Development	Delayed can pick up toys and shake rattle; good head control; tracks with eyes; no speech with tracheostomy (15 months)	Delayed sat unsupported (<13 months); walk independently (23 months); 2-word sentences but pronunciation troubles (4 years)
Other genetic testing	Congenital Heart Defect and Heterotaxy 82-gene panel: variant of uncertain significance in *ANKS6* (c.2233G>T, p.Gly745Arg) WES: pathogenic, paternally-inherited variant in *FANCA* (c.1827-1G>A)	Normal craniosynostosis gene panel

References

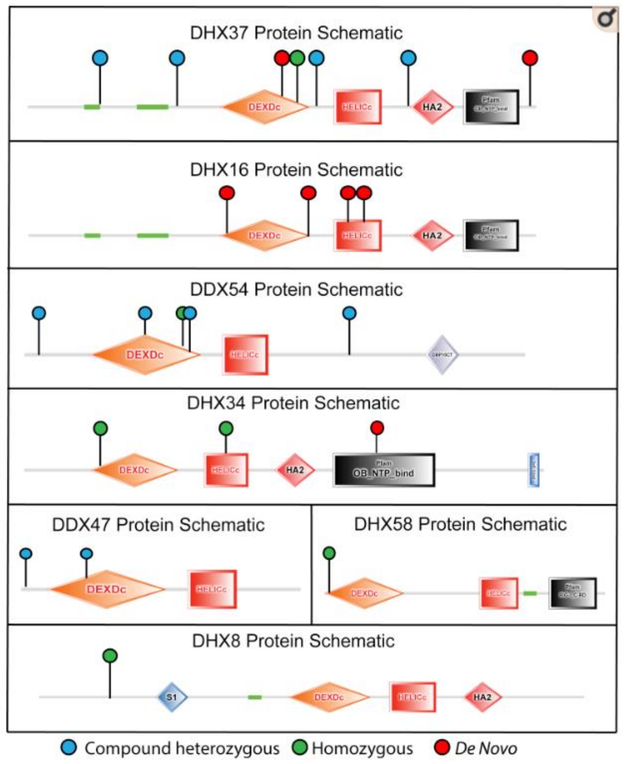
- Payne I, et al. Paralog Studies Augment Gene Discovery: DDX and DHX Genes. Am J Hum Genet. 2019 Aug 1;105(2):302-316.
- Snijders Blok L, et al. Mutations in DDX3X Are a Common Cause of Unexplained Intellectual Disability with Gender-Specific Effects on Wnt Signaling. Am J Hum Genet. 2015 Aug 6;97(2):343-52.
- https://genematcher.org/statistics. Accessed September 12, 2019.

Molecular Findings

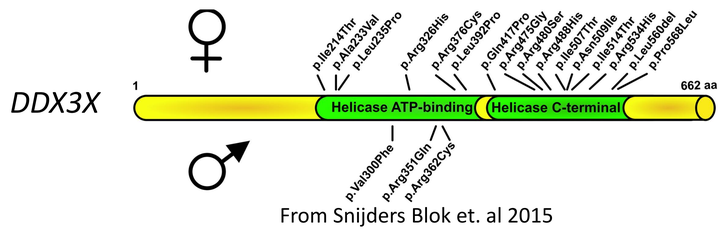
The heterozygous, *de novo* missense change, c.1019G>A (Arg340Gln), is a variant of uncertain significance by ACMGG guidelines and is found in the conserved helicase C-terminal domain.

Adapted from Payne et. al 2019

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. Pathogenic variants in other RNA helicase genes, such as *DDX3X*, *DHX30*, and *EIF4A3* have been associated with neurodevelopmental disorders that can include visceral malformations.



From Payne et. al 2019



From Snijders Blok et. al 2015

Summary

We would like to gather more patients to better describe the clinical spectrum associated with *EIF4A1* variants and reinforce the pathogenicity of similar variants. We would also like to pursue functional studies.