Expanding the Phenotype of DREAM-PL: A Case Report

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Introduction

Congenital abnormalities associated with novel variants in the *CTU2* gene (OMIM #617057) include **D**ysmorphic facies, **Re**nal agenesis, **A**mbiguous genitalia in males, **M**icrocephaly, **P**olydactyly, and **L**issencephaly. This clinical presentation has been called DREAM-PL syndrome (OMIM #618142), an acronym that highlights the observed clinical features in the founding case. Very few cases have been described in the literature (10 discovered at the time of this report), but they are consistent with autosomal recessive inheritance. There is clinical variability as well as allelic heterogeneity. The observed differences are consistent with the molecular pathway for cytosolic thiouridylase subunit 2 (*CTU2*), which is involved in the post-transcriptional modification of tRNAs, thus affecting the codon reading accuracy for multiple translational products during development. However, a high degree of pleiotropy suggests the possibility of interaction with other genes. We report a patient who may illustrate the potential influence of other gene variants on the *CTU2* phenotype.

Case Report

A four-year-old female presented with developmental delay, dysarthria, dysmorphic features, bilateral mixed hearing deficits, panhypopituitarism (ectopic posterior pituitary), hyperinsulinism, ventricular septal defect, and hemangiomas. She did not have renal agenesis, but she did have one ectopic kidney. She also lacked polydactyly, lissencephaly, or ambiguous genitals. She also displayed callosal dysgenesis, joint laxity, generalized hypotonia, and "staring episodes." The mother has a history of seizures and learning difficulties. Whole exome revealed three variants of uncertain significance (one pathogenic in the literature and inherited from the mother, the other two of uncertain origin) in the *CTU2* gene. The father has been unwilling to participate in a genetic workup thus far. There is no known consanguinity between the parents. Three other heterozygous variants of uncertain significance were noted: two in *DNAH8* (OMIM#603337) in cis and one in *DNAH5* (OMIM #603335). Both genes are associated with autosomal recessive primary ciliary dyskinesia (ARPCD) and therefore this result is not considered diagnostic for the patient.

Methods

The Invitae Congenital Heart Defects and Heterotaxy Panel, and the Invitae Disorders of Sex Development Panel were employed. A SNP Microarray Analysis on peripheral blood was also performed using the Affymetrix Cytoscan HD platform. Clinical Exome Sequence Analysis was performed on OraCollect Buccal samples via the GeneDx XomeDxPlus. Findings from the clinical assessments and genetics studies were then compared to published literature regarding the *CTU2* gene and clinical correlates. Ten patients with this diagnosis were reported in 4 different publications.

Results

Table 1: Frequencies of Features in Documented Cases

Feature	Dysmorphic facies	Renal agenesis	Ambiguous genitals (only in males)	Microcephaly	Polydactyly	Lissencephaly	Congenital Heart Defects **	Seizures **	Other brain abnormalities **	Respiratory Support Required **
Frequency (in documented cases)	10/10	**5/10**	**5/7**	10/10	**3/10**	**3/10**	8/10	7/8	10/10	6/8
Presence in Patient	+	- Ectopic kidney present	-	-	-	-	+	+	+	-

**** Indicates a potentially life-threatening or life-altering feature which is not listed as a part of DREAM-PL, but is found in over half of documented cases.**

Table 1. Phenotypic frequencies in documented cases compared to those found in this patient. Bolded fractions indicate that the frequency is concerning for use in nomenclature. In this patient, only one of the acronym's features are found, yet this patient presents with three potentially life-threatening or life-altering features that are not a part of the acronym. Polydactyly and lissencephaly have been found in three of eleven cases. Renal agenesis was found in five of eleven cases (although renal abnormalities in general may be found more frequently). Ambiguous genitals only occurs in males, and even then, it was only reported in five of seven cases.

Results (Continued)

Only three out of the six features denoted by the acronym DREAM-PL were found in over half of documented cases. Three of the now eleven patients did not survive past the neonatal stage, and therefore could not be assessed for "developmental delay." One additional patient has not been evaluated since 4 months of age, and another since 17 months. All patients had dysmorphic facial features, microcephaly, and at least one notable neurological finding. Most subjects have been male (7/11). All patients who survived long enough to be assessed revealed developmental delay. Seven of these manifested seizures. Six of them also required respiratory support. Other notable features included panhypopituitarism, bilateral mixed hearing deficits (3/11 including this case), and hyperinsulinism. Congenital heart defects include ventricular septal defect (which this patient displays), atrial septal defect, ventricular hypoplasia, and patent ductus arteriosus. An alternative acronym has been proposed: "Microcephaly, facial dysmorphism, renal agenesis, and ambiguous genitalia syndrome (MFRG, OMIM #618142).

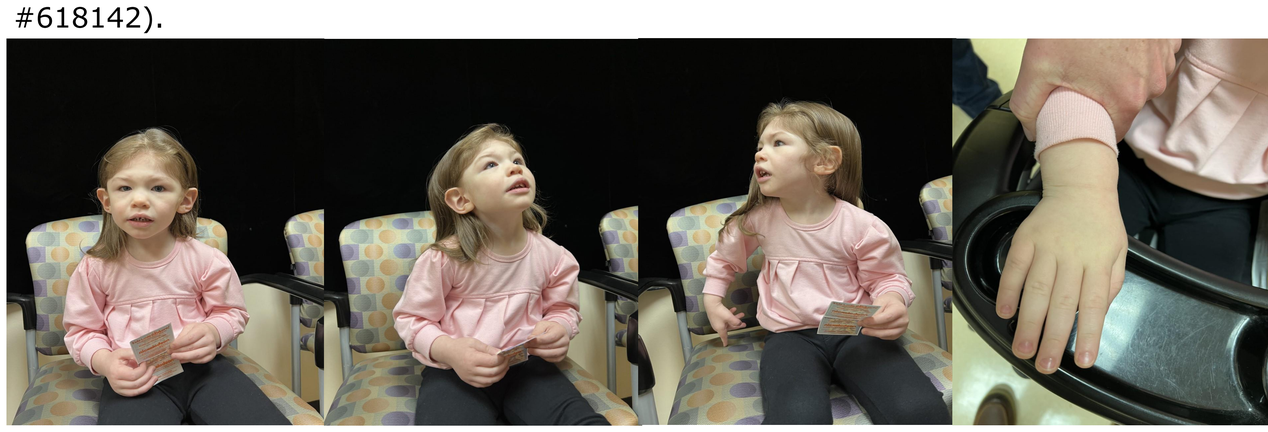

Figure 1. Clinical images of patient with down-slanting and narrow palpebral fissures, strabismus, and large prominent ears with hypoplastic pinnae. Puffy edematous hands lacked polydactyly.

Discussion

Due to the small sample size of DREAM-PL syndrome diagnoses, and its phenotypic variability, diagnosis may be difficult without genetic testing. Polydactyly and lissencephaly are each reported in only three cases. Phenotypic variability is to be expected in a disorder involving a protein that directly influences a variety of translational products. The acronym DREAM-PL is problematic, as only a fraction of the emphasized clinical features have been seen in a majority of cases. Other clinically important features have been observed and are not honored by the acronym. These include congenital heart defects and seizures, as well as other brain abnormalities such as hypoplasia of corpus callosum, pituitary hypoplasia, and unspecified white matter loss. Inconsistencies with the syndrome's acronym and actual observed phenotypes must be addressed for implications in future diagnoses.

Conclusions

- Some features (i.e. polydactly) currently associated with variants in *CTU2* could also be due to influences from other genetic abnormalities.
- We propose that it would be more appropriate to designate patients with variants in the *CTU2* gene as manifesting "*CTU2* phenotypic spectrum" and set aside the convenient, but ultimately misleading acronyms.
- More in-depth research and discussion regarding proper versus improper naming theories of new and complex genetic disorders may be necessary.

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Online Mendelian Inheritance in Man, OMIM. MIM Number 618142 Johns Hopkins University, Baltimore, MD. Entry - #618142 - MICROCEPHALY, FACIAL DYSMORPHISM, RENAL AGENESIS, AND AMBIGUOUS GENITALIA SYNDROME; MFRG - OMIM

Acknowledgments

Medical Alumni Foundation for Upstate Medical University (College of Medicine Student Reimbursement)