dependent aromatic amino acid hydroxylases, including the phenylalanine, tyrosine, and tryptophan hydroxylases. Loss of the DNAJC12 chaperone causes destabilization of these hydroxylases, leading to hyperphenylalaninemia and deficiencies of the neurotransmitters dopamine, norepinephrine, epinephrine, and serotonin. Biopterin metabolism remains normal in affected individuals. We present the case of a patient who screened positive for hyperphenylalaninemia on newborn screening (NBS) and was discovered to be homozygous for a pathogenic variant in *DNAJC12*.

Case presentation: The patient was a twin birth, born premature at 25 weeks gestation via C-section. Neonatal course was prolonged and complicated, and included mechanical ventilation, surgical closure of a patent ductus arteriosus, and hyperalimentation. Newborn screen was positive for hyperphenylalaninemia, and results of confirmatory biochemical testing confirmed mild hyperphenylalaninemia. Phenylalanine and tyrosine levels were in the therapeutic range despite hyperalimentation and subsequently an unrestricted diet with formula was recommended. Genetic testing using a commercially available laboratory involved sequencing and deletion/duplication analysis of six genes related the hyperphenylalaninemia: *PAH*, *GCH1*, *PCBD1*, *QDPR*, *PTS*, and *SPR*. Genetic testing returned negative. Cofactor screening revealed findings consistent with PAH enzyme deficiency. Additional testing was limited as compliance with onsite clinical visits was limited especially during the pandemic.

At 16 m.o., the patient had features inconsistent with a diagnosis of mild hyperphenylalaninemia and not explained by prematurity alone, including significant hypotonia, and developmental delay. She was beginning to sit up, but not pulling to stand. Fine motor skills were normal, but speech was delayed. No abnormal movements were noted. Exome sequencing was offered to exclude other genetic etiologies for her manifestations, which revealed that the patient was homozygous for a likely pathogenic variant in *DNAJC12* (NM_021800.2:c. 235C>T, p.Arg79*).

Neurotransmitter deficiency is measured by analyzing levels of neurotransmitter metabolites and precursors, including the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA), the dopamine metabolite homovanillic acid (HVA), and the levodopa metabolite 3-*O*-Methyldopa (3-OMD). Levodopa is the precursor to dopamine, epinephrine, and norepinephrine. Neurotransmitter analysis revealed severe deficiencies in 5-HIAA (26 nmol/L, reference: 129-520 nmol/L), HVA (215 nmol/L, reference: 294-1115 nmol/L) and 3OMD (6 nmol/L, reference: <300 nmol/L). Prolactin levels were elevated (42.4 ng/mL, reference: 1.40-24.00 ng/mL), indicating dopamine deficiency.

Therapy with sapropterin, levodopa/carbidopa and 5-hydroxytryptophan have been initiated. Patient continues on an unrestricted diet. Improvements in cognitive and motor functioning are evident and will be presented. Normal neurodevelopment has been reported when treatment was initiated within the first year of life. Treatment initiated early in life is integral to maintaining normal neurodevelopment and preventing neurologic defects in patients.

Conclusion: This case emphasizes the necessity of reassessing patients in which the genetic etiology for an inborn error of metabolism is unknown. During the initial genetic testing, the patient had the most comprehensive multigene panel available for hyperphenylalaninemia, which returned negative. *DNAJC12* molecular testing should be considered in all patients with hyperphenylalaninemia as this is a treatable IEM.

	1 m.o	3 m.o*	6 m.o	9 m.o	12 m.o	16 m.o**	19 m.o***	24 m.o
Phenylalanine (mg/dL)	2.7 (H)	3.7 (H)	4.3 (H)	3.6 (H)	4.5 (H)	3.9 (H)	6.2 (H)	2.7 (H)
5-HIAA (nmol/L)	—	—	—	—	—	—	26 (L)	—
HVA (nmol/L)	—	—	—	—	—	—	215 (L)	—
3OMD (nmol/L)	—	—	—	—	—	—	6	—
Prolactin (nmol/L)	—	—	—	—	—	—	42.4 (H)	—

*Initial consultation with genetics.
**reassessment by genetics.
***after diagnosis of *DNAJC12*-related hyperphenylalaninemia.

https://doi.org/10.1016/j.gim.2022.01.049

eP012

Biochemical characterization of single minded-1 missense variants associated with severe obesity

Megan Vogel[1], Ida Moeller[1], Alastair Garfield[1], Bhavik Shah[1]

[1]*Rhythm Pharmaceuticals, Inc, Boston, MA*

Introduction: Single Minded-1 (SIM1) is a transcription factor involved in development and function of the hypothalamic paraventricular nucleus, a site critical for the body weight–regulating function of the melanocortin-4 receptor (MC4R) pathway. Consistent with its MC4R pathway involvement, rare loss-of-function (LOF) variants in *SIM1* are associated with severe early-onset obesity and hyperphagia, hallmark features of rare genetic diseases of obesity. To better understand the contribution of *SIM1* variants to severe clinical obesity, we performed functional biochemical characterization of rare *SIM1* variants in Rhythm's database of approximately 40,000 individuals with severe obesity.

Methods: Functional impact of *SIM1* missense variants was assessed using a well-established and controlled hypoxia response element- (HRE-) luciferase reporter gene assay.

Results: In total, 213 missense *SIM1* variants were identified in individuals with severe obesity; 93 have not been previously described, while 197 have not been functionally assessed. Biochemical characterization of all 213 *SIM1* variants was performed to determine impact on protein function. Of the 213 variants, 3 exhibited complete LOF, 93 exhibited moderate LOF, and 117 exhibited WT-like activity. Thus, nearly half of the rare *SIM1* missense variants, including 40 novel variants, observed in obese individuals exhibit LOF in a biochemical assay.

Conclusion: These findings provide important insights into the *SIM1* variant landscape and may help in the future diagnosis and treatment of individuals with SIM1 deficiency obesity.

https://doi.org/10.1016/j.gim.2022.01.050