rearrangements, especially in the heterozygous state, could lead to a delayed or even missed diagnosis. For example, if the deletion described in this case was *in cis* with missense change in *GALNS*, NGS would label the patient as a heterozygote rather than affected. Our case highlights the benefit of biochemical analysis for lysosomal storage disorders in cases with equivocal or incomplete molecular analysis. Molecular analysis is useful to confirm a biochemical diagnosis and assist with genetic counseling and future prenatal testing and carrier testing. Recognizing limitations of molecular testing is important to ensure accurate diagnosis and treatment for individuals with Morquio syndrome in a timely manner.

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eP010

Conservative management with serial biochemical monitoring for newborn screen detected Maple Syrup Urine Disease (MSUD) patients without metabolic decompensation

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Background: Maple syrup urine disease (MSUD) is a rare inborn error of metabolism characterized by deficiency of branched-chain alpha-keto acid dehydrogenase that metabolizes the three branched-chain amino acids (BCAAs) leucine, isoleucine, and valine. The result of this enzyme deficiency is a toxic buildup of metabolites, typically within the first 24-48 hours of life. The main neurotoxic effects are due to accumulation of large amounts of leucine which can lead to severe cerebral edema. Treatment requires immediate medical intervention to lower leucine levels. Various techniques have been used to reduce plasma leucine levels including invasive techniques such as dialysis and continuous renal replacement therapy. Risks are associated with such techniques including infections, hypovolemia, electrolyte disturbances, and fluid overload. These risks must be balanced with the risk of cerebral edema and neurologic side effect of metabolic intoxication from high leucine levels. Whatever the means, the goal remains rapid reduction in leucine levels.
Case presentation: We present two cases of patients with MSUD ascertained by abnormal newborn screens. Their initial leucine levels were critically elevated but showed no evidence of decompensation. They were both able to be successfully managed with conservative interventions to safely reduce leucine levels. Patient #1 is a 3-month-old male infant identified on newborn screen on the 5th day of life. Confirmatory testing drawn on the 6th day of life which revealed a Leucine level in the critical range of 2022 µmol/l. He was admitted to the hospital the same day for emergent management. The baby was doing well, gaining weight and neurologically intact. He was managed conservatively with a BCAA restricted formula, MSUD Anamix Early Years, intravenous fluids with D10, and NS to maintain Na greater than 137. We were able to safely reduce leucine levels by 39% within the first 24 hours and a 94% reduction within 72 hours, resulting in normalization of leucine levels to normal range of 109 µmol/l. At this time, it was indicated to add isoleucine and valine back into the diet, but the facility's pharmacy did not stock these amino acid supplements. Therefore, we used IVA Anamix Early Years formula, which is leucine free but contained our desired isoleucine and valine. This was utilized until we received shipment of isoleucine and valine supplements. On day 4 of admission, natural protein was able to be safely reintroduced and appropriately formulated branch amino acid supplement shipments were received. He was monitored with daily plasma amino acids for a total of 7 days to ensure stability before being discharged. He continues to be routinely followed in our clinic on a weekly basis and is doing well. He is thriving with a current weight of 7.1kg and length of 61.5cm. He was molecular testing confirmed to have biallelic pathogenic missense variants in trans in the *BCKDHB* gene (NM_183050.4). These changes were identified as c.410C>T (p.Ala137Val) and c.1A>T (p.Met1?). He has no obvious neurologic deficits.
Patient #2 is a 5-year-old boy also identified on newborn screen on the 4th day of life. Confirmatory labs draw on that same day revealed a leucine level of 1846 µmol/l. He had a similar course with similar results. He was managed conservatively with a leucine free diet and intravenous fluids. Also, in this case, there was a delay in shipment of supplemental isoleucine and valine, so natural protein was initiated earlier on the 3rd day of hospitalization due to a critically low valine level. While this may have slowed the rate of decline of leucine levels, we were still able to achieve a 32% reduction in leucine within the first 48 hours of hospitalization and stabilization for discharge was achieved within a week to a level of 167 µmol/l. He has since been able to receive a liver transplantation at one year of age and remains neurologically intact. Subsequent molecular testing has revealed that he carries a homozygous 213.22 kb deletion in BCKDHB gene which was consistent with the reported consanguinity of parents being second cousins.
Conclusion: Advances in newborn screening and early detection has modified the disease progression in patients with MSUD. When a patient is diagnosed before metabolic decompensation, without proteolysis, the reducing of leucine can be quickly and successfully achieved without invasive measures. The success of these interventions can be assessed by clinical presentation, CMP, and frequent monitoring of plasma amino acids. As demonstrated in our patients, daily reduction is 600-750 µmol/l vs historical patients admitted with symptoms, average dropping 300-350 µmol/l. Our two patients with MSUD demonstrated the evidence that, without metabolic crisis, conservative management of high leucine levels can result in safe and timely reduction of leucine with no apparent neurologic sequela. While each case must be considered individually, these cases may change our standard approach. It may at least present an alternative approach in circumstances where continuous renal replacement therapy or a form of dialysis may not be readily available for a neonatal patient provided levels can be readily monitored to ensure an adequate decline in levels.

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eP011

Diagnosis of *DNAJC12*-deficient hyperphenylalaninemia offers targeted therapeutic options to counteract neurotransmitter deficiency

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Background: *DNAJC12*-related hyperphenylalaninemia is a recently described inborn error of metabolism (IEM) associated with hyperphenylalaninemia and neurotransmitter deficiency, caused by biallelic pathogenic variants in the *DNAJC12* gene. Clinical features include global developmental delay, intellectual disability, autism spectrum disorder, and dystonia. *DNAJC12*-encoded protein functions as a chaperone facilitating the proper folding of the biopterin-

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.

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eP012

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

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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.

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