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Commentary

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Laboratory and Genotype Relationship of Patients with SDHA-Related Mitochondrial Disease

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Succinate dehydrogenase deficiency · Mitochondrial disease · Leigh syndrome phenotype · Whole-exome sequencing · Metabolic diseases

In this paper, we aim to explain the comment written about our article "Two Patients Diagnosed as Succinate Dehydrogenase Deficiency: Case Report" [Ürey et al., 2023]. First patient has minimal lactate excretion in urine organic acid analysis (lactic acid 2.45 mmol/mol crea) and normal blood lactate level (lactate 1.80 mmol/L). For patient 2, repeated measurement of serum lactate confirmed the high baseline value. Blood lactate levels range from 41.3 to 67.4 mg/dL (nv: 4.5–19.8). Urine organic acid analysis also revealed severe excretion of lactic acid levels which range from 354.75 to 911 mmol/mol cre. She presented clinically with symptoms of metabolic acidosis such as tachypnea, impaired conciousness, nausea, emesis, tiredness, or headache. Patient 1 was described with encephalopathy due to neuroradiological findings detected at the age of one year. MRI revealed findings of Leigh's encephalopathy and clinically seizures, hypotonia, and lethargy. She has muscle wasting. Her weight was 48 kg and height was 152 cm when she was 21 years old. Needle electromyography was nonspecific when done at 10 years old. Muscle biopsy revealed signs of mitochondrial cytopathy and muscle homogenate was tested for respiratory functions and revealed complex II deficiency.

We classified the variants not only with in silico variant effect prediction tools but also in light of the recommended criteria and guidelines of the American College of Medical Genetics and Genomics about variant interpretation (a total of 26 criteria of which 14 of them are pathogenic and 12 of them are benign, 2015 at four evidence levels; very strong, strong, moderate, and supporting) [Richards et al., 2015]. We used the PM2 (absent in controls) and PP3 (in silico tools have pathogenic prediction) as moderate criteria (4 points), and PP4 (patients' phenotype and MRI findings support the disease) as supporting criteria (1 point) for both of the two variants (variants NM_004168.4:c.1328G>A [p.Cys443Tyr] and NM_004168:c.872A>C [p.Glu291Ala]) detected in patient 1. Segregation analysis applied for mother, father, and patient revealed the compound heterozygosity of the variants (trans-position). Three of the unaffected siblings had only heterozygous variants. We did not use PP1 (cosegregation of the variants in multiple affected patients in a family) criteria because of the lack of additional affected patients in the family. But a comprehensive refinement of the ACMG guidelines recommends using PP1 criteria if there is biochemical or radiological

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evidence of a specific disease [Nykamp et al., 2017]. When PP1 is used as a supporting criterion, two of the variants could be reclassified as likely pathogenic supporting the clinical relevance. In patient 2, the current criteria have been also used for interpreting the variants. The first variant (NM_004168:c.1946del) results in a premature termination codon that is predicted to cause a truncated protein (PVS1 criterion was used as strong pathogenicity evidence). The other used criteria were PM2, PP1, and PP4 as described above. So the first variant is classified as "likely pathogenic." Regarding patient 2 and the variant localized in an intron (NM_004168:c.1909-12_1909-11del), we apologize for not providing a clear explanation in the article. While intronic variants are generally considered noncoding, they can still have functional implications through splicing or regulatory mechanisms. However, we also recommend that it is better to support the pathogenicity of this intronic variant with additional studies, such as RNA analysis or computational prediction of splicing alterations. We agree that further investigations, such as functional studies or biochemical analysis would greatly contribute to confirming the causative nature of these variants. However, we support and claim these variants are the causative ones of our patient's phenotype.

Conflict of Interest Statement

The authors have no conflicts of interest to report.

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Author Contributions

Burcu Civelek Ürey has collected the clinical and laboratory data of the patient and written the manuscript. Ahmet Cevdet Ceylan and Büşranur Çavdarlı have been involved with molecular analyses and its interpretation. Oya Kıreker Köylü, Burak Yürek, and Çiğdem Seher Kasapkara have collected the clinical data. Ayşegül Neşe Çıtak Kurt has collected the neurologic data from the patient.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, B.C.U., upon reasonable request.

References

Nykamp K, Anderson M, Powers M, Garcia J, Herrera B, Ho YY, et al. Sherloc: a comprehensive refinement of the ACMG-AMP variant classification criteria. Genet Med. 2017;19(10):1105–17.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of medical Genetics and Genomics and the association for molecular pathology. Genet Med. 2015;17(5):405–24.

Ürey BC, Ceylan AC, Çavdarlı B, Çıtak Kurt AN, Köylü OK, Yürek B, et al. Two patients diagnosed as succinate dehydrogenase deficiency: case report. Mol Syndromol. 2023 Apr;14(2):171–4.