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Molecular diagnosis of MCAD in the Macedonian neonates with elevated medium-chain acylcarnitines identified through MS/MS-based newborn screening

Violeta Anastasovska[1], Mirjana Kocova[2], Nikolina Zdraveska[3], Tine Tesovnik[4], Maruša Debeljak[4], Jernej Kovač[4]

[1]Department of Neonatal Screening, University Clinic for Pediatrics, Ss. Cyril and Methodius University in Skopje, Faculty of Medicine, Republic of North Macedonia

[2]Medical Faculty, Ss. Cyril and Methodius University in Skopje, Faculty of Medicine, Republic of North Macedonia

[3]Department of Neonatology, University Clinic for Pediatrics, Ss. Cyril and Methodius University in Skopje, Faculty of Medicine, Republic of North Macedonia

[4]Clinical Institute for Special Laboratory Diagnostics, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia

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Background/Objectives:

Medium Chain acyl-CoA dehydrogenase (MCAD) deficiency is an autosomal recessive disorder of fatty acid oxidation, with potential fatal outcome. It is diagnosed by acylcarnitine analysis on newborn screening blood spot cards by tandem mass spectrometry. Early diagnosis of MCAD and presymptomatic treatment can potentially reduce morbidity and mortality.

Materials and Methods

A total of 38,578 newborns were screened for inborn errors of metabolism during May 2014 - Jan 2022, using the LC/MS/MS method. Eight newborns showed elevations of medium-chain acylcarnitines with predominance of octanoylcarnitine, and C8/C10 ratio as well. Molecular *ACADM* gene analysis was performed by whole exome sequencing using NovaSeq 6000 (Illumina), and confirmed by Sanger sequencing. Sequencing data were analysed using the bcbio_nextgen bioinformatics pipeline (version 1.2.7; GRCh37 genome).

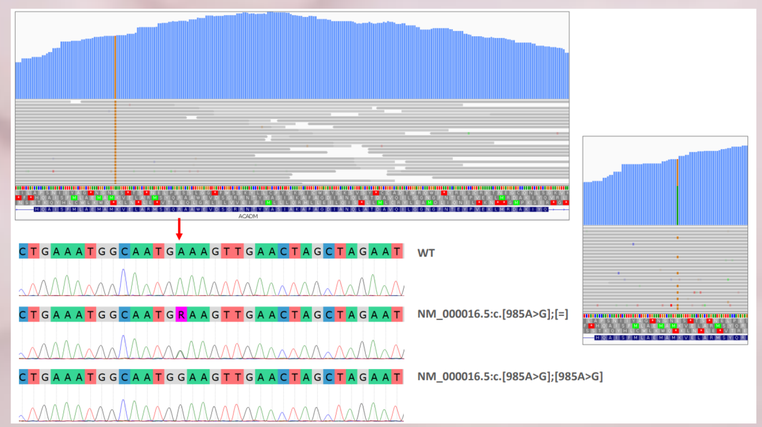

Figure 1. The c.958A>G mutation in the ACADM gene

Results

Molecular analysis of the *ACADM* gene was performed in eight patients with positive metabolic screening for MCAD deficiency. Two different *ACADM* mutations were obtained in 93.75% of the alleles. The common c.958A>G mutation (p.Lys329Glu), Fig. 1, was detected in 12/16 (75%) alleles, while 3/16 (18.75%) alleles had c.244dupT pathogenic variant (p.Trp81fs), Fig. 2. Five of the patients were homozygous for c.985A>G variant, and one was homozygous for c.244dupT. One of them was compound heterozygote (c.985A>G/c.244dupT) while another was only heterozygote for c.958A>G without detection of the second mutant allele.

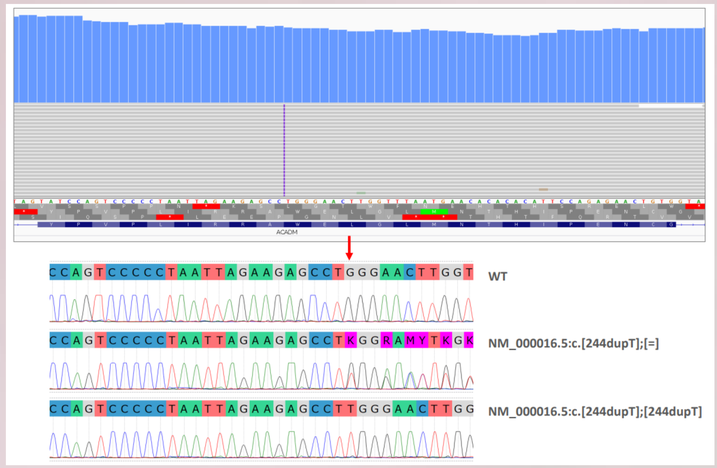

Figure 2. The c.244dupT mutation in the ACADM gene

Conclusions

The sensitivity of medium-chain acylcarnitines as screening markers for early detection of MCAD was confirmed through the molecular analysis of the *ACADM* gene. Early detection and treatment have successfully prevented adverse health outcomes in patients with MCAD.

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