CNV Analysis of ACADM Enhances Yield in the Molecular Diagnosis of Medium-Chain Acyl-CoA Dehydrogenase Deficiency
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Abstract

Background: Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is one of the most common recessively inherited metabolic diseases. The condition is caused by pathogenic mutations in the medium-chain acyl-CoA dehydrogenase gene (ACADM) that affect the β-oxidation of fatty acids 6–12 carbons long. Affected individuals are unable to generate sufficient ketones for energy during periods of glucose and glycogen depletion and can experience extreme hypoglycemia. Untreated episodes can lead to coma and death. Adverse outcomes can be prevented by avoiding metabolic stress and follow ing appropriate food intake schedules and emergency protocols. Molecular confirmation of biallelic ACADM mutations signifies the diagnosis of MCADD in individuals with positive newborn screening (NBS) results and further justifies medical interventions.

Methods: In this study, DNA samples from individuals who were positive for MCADD at NBS or had suspected ACADM-related conditions were analyzed with next-generation sequencing (NGS), which included deletion/duplication analysis.

Results: The spectrum of Likely Pathogenic/Pathogenic (LP/P) mutations involved copy number variants (CNVs) and missense, frameshift, and intronic variants. Two novel variants identified in these individuals were both subgenic CNVs, including the first ACADM duplication variant: duplication of exon 8. The c.985A>G (p.Lys329Glu) variant, a known common mutation, was the most frequently observed variant in the study group. Notably, a significant fraction of individuals had subgenic CNVs that would have been missed in tests using traditional NGS methods and cytogenetic arrays.

Conclusions: ACADM CNV detection expands the mutation spectrum of MCADD and improves the yield of MCADD molecular diagnosis and therefore should be a routine practice in MCADD diagnosis and confirmation.

Introduction

Study group: Fifteen individuals who tested positive for MCADD at NBS or had suspected MCADD-related conditions were studied.

Demographics of the study group

Table 1. Variants classified in study group by mutation type (A, B) and variant combination (C) (B) Variant types of ACADM LP/P mutations (relative proportion)

Results

Table 2. Mutation spectrum of ACADM

Table 1A shows the distribution of variant types by classification in the study group.

Table 1B shows that CNVs comprised 27% of LP/P ACADM mutations identified in the study group, second to missense mutations (45%).

Table 1C shows the allele combinations of variants identified in the study group. LP/P ACADM variants were identified in 73% of the individuals in the study group.

Conclusions

- CNVs are a major component of the ACADM pathogenic mutation spectrum.
- ACADM CNV detection expands the mutation spectrum of MCADD.
- ACADM CNV detection improves the yield of MCADD molecular diagnosis.
- ACADM CNV detection should be a routine practice in MCADD diagnosis and confirmation.

References