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Molecular Study and Mutational Analysis of Glutaric Aciduria Type I in Egyptian infants

By

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For Fulfillment of Master Degree in Biochemistry

(B.Sc. in Biochemistry)

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CONTENTS

Abstract

Glutaric aciduria type I (GAI) is an autosomal recessive disorder characterized by a deficiency of glutaryl-CoA dehydrogenase (GCDH). GAI is one of the treatable metabolic disorders characterized by macrocephaly, acute encephalitis-like crises, dystonia and characteristic frontotemporal atrophy. In this study, the clinical, biochemical and molecular profile of twenty one patients with GAI from twenty one unrelated families from Egypt were carried out. RNA was extracted from whole blood for synthesis of cDNA, the fragment of GCDH was amplified and sequenced. In this study, a total of 15 different mutations were reported between Egyptian families ranging from missense, nonsense, frame shift and silent mutations. A five novel mutations in GCDH gene (c.148T>A (p.Trp50Arg), c.158C>A (p.Pro53Gln), c.1284C>G (p.Ile428Met), c.644_645insCTCG (p.(Pro217Leufs*14) and c.1189G>T (p.Glu397*)) were reported. In addition to seven mutations have been published previously and 3 silent mutations in 3`-UTR region. It is clear that out of 21 patients Exons 4 (3 mutations/3 patients), 6 (3 mutations/4 patients), 8 (2 mutations/4 patients) and 11(2 mutations/8 patients) are hot spot regions of GCDH gene representing 14%, 20%, 20% and 38% respectively of patients. Molecular confirmation is helpful in providing genetic counseling and prenatal diagnosis in subsequent pregnancy. An early diagnosis and timely intervention can improve the underlying prognosis.

List of Abbreviations

ACDs	Acyl-CoA dehydrogenases
BBB	Blood brain barrier
BLAST	Basic Local Alignment Search Tool
BLASTN	Nucleotide homology search
BlASTP	Protein homology search
CAT	Cationic amino acid transporter
CPTII	Carnitine palmitoyl transferase II
C5DC	Glutaryl carnitine/ C5 dicarboxylic carnitine
CSF	Cerebrospinal fluid
cDNA	complementary deoxyribonucleic acid
DNA	Deoxyribonucleic acid
EDTA	Ethylene diamine tetra acetic acid
ETBr	Ethidium bromide
FAD	Flavin adenine diphosphate
GC-MS	Gas chromatograph-mass spectrometry
GA	Glutamic aciduria /Glutaric acid
GAI	Glutaric aciduria type I
GCDH	Glutaryl-CoA Dehydrogenase
GAII	Glutaric aciduria type II
GAIII	Glutaric aciduria type III
gDNA	Genomic deoxyribonucleic acid
HPLC	High performance liquid chromatography
HGMD	The Human Gene Mutation Database
IEM	Inborn Errors of Metabolism
IMD	Inherited metabolic disorders
KD	Kilo Dalton
LC/MS	Liquid chromatograph-mass spectrometry
MRI	Magnetic Resonance Imaging
mRNA	Messenger ribonucleic acid
NCBI	National Center for biotechnology information
OADs	Organic acid disorders
OAs	Organic acidurias

ODC	Oxodicarboxylate carrier
OGC	Oxoglutarate carrier
ORC1	Ornithine carriers
ORF	Open reading frame
PCR	Polymerase Chain Reaction
PDH	Pyruvate dehydrogenase
r.p.m	Round per minute
TBE buffer	Tris-Borate EDTA buffer
UTR	Untranslated Region
α-KG	α-ketoglutarate
3-OHGA	3-hydroxyglutaric acid

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