بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

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قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

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تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

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Genotype-Based Estimation of tetrahydrobiopterin among Egyptian children patients with atypicalphenylketonuria.

A Thesis Submitted by

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Abstract

Phenylketonuria(PKU) is an autosomal recessive inherited inborn error of metabolism that results from the impairment of phenylalanine hydroxylases(PAH)action due to either a mutation in PAH- gene which lead to nonfunctional enzyme or a defect in the Enzyme co-factor tetrahydrobiopterin(BH4) biosynthesis (Atypical PKU) (Malignant PKU), the main cause of BH4 biosynthesis defect is the 6-pyrovoil tetrahydrobiopterin syntheses (PTPS-gene) mutations . To determine the mutation spectrum in coding region of PTPS-gene of atypical PKU Egyptian patients, complete RNA was extracted and purified and PTPS cDNA was synthesized and purified for double stranded sequencing in both direction. A total of 6 mutations were detected in PTPS-gene, four of them were Novel Mutations, one deletion mutation(c.164_186del (p.Val55Aspfs*2)cause deletion of all of exon 3, Two missens mutations caused benign mutation c.86A>T(p.Lys29Ile) andc.22C>T(p.Arg8Cys), one substitution mutation in exon-5 giving the same amino acid c.273G>A(p.91Lys=). The only two mutations were previously reported, a substitution mutation cause pathogenic mutation in exon-4 c.200C>T(p.Thr67Met) and a synonymous mutation c.405T>C(p.135Thr=) in exon-6. Identification of these mutations in atypical PKU Egyptian patients will facilitate differential confirmatory diagnosis, which is important for appropriate treatments. It will also aid carrier detection, genetic counseling, and subsequent prenatal diagnosis among Egyptian families who have history of disease.

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List of abbreviations

IEMs	Inborn errors of metabolism
3-MCC	3-methylcrotonyl-CoA carboxylase deficiency
3MG	3-methylglutaconyl-CoA hydratase deficiency
5HIAA	5-hydroxyindoleacetic acid
AADC	aromatic amino acid decarboxylase
AMT	amino-methyl-transferase
AR	aldose reductase
BCAAs	branched-chain amino acids
BCKDC	branched-chain alpha-keto acid dehydrogenase complex
BH2	dihydrobiopterin
BH4	tetrahydrobiopterin
BIO	biotinidase or holocarboxylase synthetase deficiency
BKT	β-ketothiolase deficiency
BSA	bovine serum albumin
CACT	Carnitine acylcarnitine translocase
cAMP	Cyclic adinosine Monophosphate
Carnitine	3-hydroxy-4-(N,N,N-trimethylammonio)butanoate
CDG	congenital disorders of glycosylation
cGMP	Cyclic guanosine Monophosphate
CID	collision-induced dissociation
CPT I	carnitine palmitoyltransferase I
CPT II	carnitine palmitoyltransferase II
CPT II/CACT	carnitine palmitoyltransferase II/carnitine-acylcarnitine translocase deficiency
CPT1A	carnitine palmitoyltransferase I deficiency,
CR	carbonyl reductase
CT	computed tomography
CUD	carnitine uptake deficiency,
DBS	Dried Blood spots
DHFR	dihydrofolatereductase
DLD	dihydrolipoamide dehydrogenase
EE	ethylmalonic encephalopathy
eNOS	endothelial nitric oxide synthase
FAH	fumaryl-acetoacetate hydrolase
FAO	Fatty acid Oxidation

GA1	glutaric aciduria type 1
GC/MS	gas chromatography/mass spectrometry
GCS	glycine cleavage system
GCSH	glycine cleavage system hydrogen carrier
GLDC	Glycine decarboxylase
GTP	guanosine triphosphate
GTPCH	guanosine triphosphate cyclohydrolase
HADH	3-hydroxyacyl-CoA dehydrogenase
HGD	homogentisate dioxygenase
HHC	Hereditary hemochromatosis
HIBCH	3-hydroxyisobutyryl-CoA hydrolase deficiency
HMG	3-hydroxy-3-methylglutaryl-CoA lyase deficiency
HPLC	High performance liquid chromatography
HPPD	4-hydroxy-phenylpyruvate dioxygenase
HT-1	hepatorenal tyrosinemia type 1
HVA	homovanillic acid
IBD	isobutyryl-CoA dehydrogenase deficiency
iNOS	Inducible nitric oxide synthase
IVA	isovaleryl-CoA dehydrogenase deficiency
Kuvan®	sapropterin dihydrochloride (a synthetic formulation of the 6R-isomer of BH4)
LCHAD	long-chain 3- hydroxyacyl-CoA dehydrogenase
LCHAD/TFP	longchain L-3-hydroxyacyl-CoA dehydrogenase/trifunctional protein deficiency
MAD	multiple acyl-CoA dehydrogenase deficiency
MAMAD	Malonic aciduria malonyl-CoA decarboxylase deficiency
MCAD	medium-chain acyl-CoA dehydrogenase deficiency
MCT	supplementation with medium-chain triglycerides
MHBD	2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency
MMA	methylmalonic acidemia,
MSUD	Maple syrup urine disease
NADK2	dienoyl-CoA reductase deficiency caused by mitochondrial NAD kinase 2 deficiency
NBS	Newborn screening
NKH	Non-ketotic hyperglycinaemia
nNOS	neural nitric oxide synthase

NO	nitric oxide
NOS	nitric oxide synthase
nsSNPs	Non synonymous single nucleotide polymorphisms
NTBC Nitisinone Orfadin®.	2-(2-nitro-4-trifluoro-methylbenzyol) 1,3 cyclohexanedione
P	phosphate
PA	propionic acidemia,
PAH	phenylalanine hydroxylase
PAL	phenylalanine ammonia-lyase
PCD	pterin-4a-carbinolamine dehydratase
Phe	phenylalanine
PKU	Phenylketonuria
PTPS	6- pyruvoyl-tetra hydrobiopterin synthase
SBCAD	short/branched-chain acyl-CoA dehydrogenase deficiency
SCAD	short-chain acyl-CoA dehydrogenase
SR	sepiapterinreductase
SUCLA	succinyl-CoA ligase deficiency,
TAT	tyrosine aminotransferase
TFP	Trifunctional protein
TH	tyrosine hydroxylase
TMS LC/MS/MS MS/MS	Tandem Mass Spectrometry
TrpH	tryptophan hydroxylase
TTI	Tyrosinemia type I
Tyr	tyrosine
TyrH	tyrosine hydroxylase
VLCAD	very long–chainacyl-CoA dehydrogenase deficiency
δ-ALA	5-aminolevulinic acid
LNAAs	large neutral amino acids
IEMs	Inborn errors of metabolism