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The first founder *DGUOK* mutation associated with hepatocerebral mitochondrial DNA depletion syndrome

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ABSTRACT

Deoxyguanosine kinase (dGK) deficiency is a frequent cause of mitochondrial DNA depletion associated with a hepatocerebral phenotype. In this study, we describe a new splice site mutation in the *DGUOK* gene and the clinical, radiologic, and genetic features of these *DGUOK* patients. This new *DGUOK* homozygous mutation (c.444-62C>A) was identified in three patients from two North-African consanguineous families with combined respiratory chain deficiencies and mitochondrial DNA depletion in the liver. Brain MRIs are normal in *DGUOK* patients in the literature. Interestingly, we found subtentorial abnormal myelination and moderate hyperintensity in the bilateral pallidi in our patients. This new mutation creates a cryptic splice site in intron 3 (in position −62) and is predicted to result in a larger protein with an in-frame insertion of 20 amino acids. *In silico* analysis of the putative impact of the insertion shows serious clashes in protein conformation: this insertion disrupts the α5 helix of the dGK kinase domain, rendering the protein unable to bind purine deoxyribonucleosides. In addition, a common haplotype that segregated with the disease in both families was detected by haplotype reconstruction with 10 markers (microsatellites and SNPs), which span 4.6 Mb of DNA covering the *DGUOK* locus. In conclusion, we report a new *DGUOK* splice site mutation that provide insight into a critical protein domain (dGK kinase domain) and the first founder mutation in a North-African population.

Introduction

DGUOK (deoxyguanosine kinase, dGK), *MPV17*, and *POLG* (polymerase gamma) mutations are the major causes of mitochondrial DNA (mtDNA) depletion associated with hepatocerebral syndrome [1]. Patients with dGK deficiency typically present with liver dysfunction at birth or within a few months, with or without neurological impairment, and most die before 4 years of age due to liver failure [2–6]. Subjects can have elevated serum tyrosine or phenylalanine [6]. Neurological disease may be apparent by the presence of nystagmus, developmental delay, or profound hypotonia. MRI in *DGUOK* patients is usually normal before 1 year [2,6]. However, magnetic resonance spectroscopy (MRS) can reveal a lactate peak [2,6]. Genotype–phenotype correlation studies show that patients who harbor null mutations in the *DGUOK* gene usually have early onset liver failure and significant neurological disease and die before 2 years of age [6]. Patients carrying missense mutations usually have isolated liver disease and live to the age of four without liver transplants [6]. The presence of significant neurological signs should preclude the consideration of liver transplantation [7].

dGK is a member of the deoxyribonucleoside kinase family involved in phosphorylation of deoxyribonucleosides. In mammals, there are four deoxyribonucleoside kinases with overlapping specificities: two cytoplasmic enzymes, thymidine kinase 1 (TK1) and deoxycytidine kinase (dCK), and two mitochondrial enzymes, thymidine kinase 2 (TK2) and deoxyguanosine kinase (dGK). The human dGK protein is highly specific for purine substrates [8]. Johansson et al. crystalized dGK as a dimeric protein [8]. Each monomer has an αβ architecture (with nine α helices) with a central five-stranded parallel sheet [8]. Here, we describe the clinical, radiological, and biological features of three children with

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hepatocerebral syndrome carrying the same new *DGUOK* mutation and report the first founder mutation in two North-African families.

Patients and methods

Patients

Patient 1, the second son of consanguineous Moroccan parents, was born after a normal pregnancy and term delivery (birth weight: 3260 g, height: 51 cm, OFC: 36 cm). He had a healthy older brother. At 3 months of age he presented with feeding difficulties, hypotonia, growth retardation, liver enlargement, cholestasis, and cytolysis. His brain MRI was normal. At 12 months of age, laboratory screening showed severe lactic acidosis (blood lactate: 4–7.6 mM, $N < 1.7$ mM) and high serum glycine levels but normal tyrosine levels. A urinary amino acid assay showed generalized hyperaminoaciduria. His aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma glutamyltransferase (γGT) were elevated (AST 116 IU/L, ALT 59 IU/L, γGT 103 IU/L, with reference ranges: AST < 55 IU/L, ALT < 40 IU/L, GGT < 25 IU/L). At this age, his brain MRI showed moderate hyperintensity in the bilateral pallidi and subtentorial delayed myelination. Subtentorial atrophy with ventricular dilatation was also observed (Fig. 1A). Echocardiographic examination showed moderate septal hypertrophy and mild cardiomyopathy. His condition progressively worsened and he died at 14 months of age. Histopathological examination of the liver showed lipidosis. Patient 2, the younger brother of patient 1, had a similar clinical course and died at 3 months of age. The brain MRI for patient 2 was normal.

Patient 3, a boy, was born at term as the third child of consanguineous Tunisian parents after a normal pregnancy and term

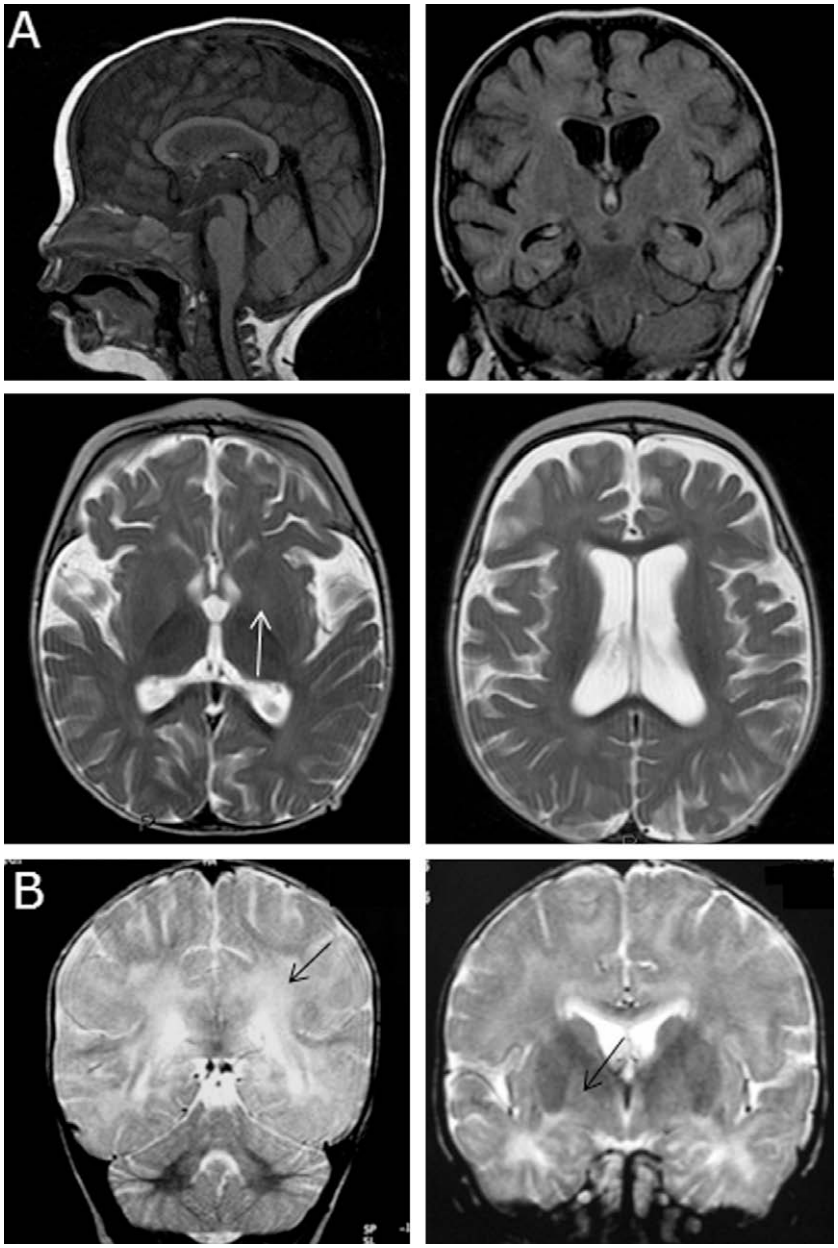

Fig. 1. Brain magnetic resonance imaging (MRI) of patients 1 (A) and 3 (B). (A) Moderate hyperintensity in the bilateral pallidi (arrow) was observed for patient 1 with subtentorial delayed myelination for this age and subtentorial atrophy with ventricular dilatation. (B) Images of patient 3 revealed a severe subtentorial leukodystrophy (arrow). In addition, a moderate hypersignal was observed in the bilateral pallidi (arrow).