New and known mutations associated with inborn errors of metabolism in a heterogeneous Middle Eastern population

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ABSTRACT

الأهداف: تحديد الطفرات المسببة لعدد من الاضطرابات الاستقلابية الخلقية بين مقيمي الإمارات العربية المتحدة.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في مستشفة توام، العين، الإمارات العربية المتحدة وذلك خلال الفترة من أبريل 2009م إلى سبتمبر 2010م، وشملت 30 مريضاً و26 فرداً من الأهالي. لقد قمنا باستخدام التشخيص الجزيئي وأدوات المعلوماتية الحيوية بما في ذلك تحديد تسلسل الحمض النووي لعدد من الجينات من أجل اكتشاف الطفرات المسببة لعدد من الاضطرابات الاستقلابية الخلقية.

النتائج: أشارت نتائج الدراسة إلى اكتشاف 7 طفرات جديدة ومسببه لعدة من الأمراض الاستقلابيه بين سكان الإمارات العربية المتحدة، كما وتشير النتائج إلى وجود 19 طفرة كانت قد ظهرت سابقاً في مجتمعات أخرى. وقد سببت هذه الطفرات الجينية عدداً من الأمراض الاستقلابية مثل: داء بيلة الفينول كيتون، وداء بول شراب القيقب، وداء اختزان الغليكوجين، وداء نقص بيتا كيتوثيوليز، وداء ذو الفقار.

خاتمه: لقد حددنا باستخدام التشخيص الجزيئي عدداً من الطفرات المسئولة عن بعض الأمراض الاستقلالبية الوراثية بين سكان دولة الإمارات العربية المتحدة والذين ينتمون إلى أصول اثنيه مختلفة. وأثبتت الدراسة مدى انتشار زواج الأقارب بين هذه الحالات، ولهذه الدراسة أهمية كبيرة حيث أنها سلطت الضوء على كيفية الوقاية من الاضطرابات الوراثية وذلك ليس في الإمارات العربية المتحدة فحسب بل في مختلف أنحاء العالم التي يكثر فيها زواج الأقارب أو يسكنها العرب والآسيويون.

Objectives: To identify the mutations underlying a number of inborn errors of metabolism (IEM) disorders among United Arab Emirates (UAE) residents.

Methods: Molecular diagnostic and bioinformatics tools were used to identify the causative mutations of IEM disorders from multi-ethnic patients residing in UAE. The study was conducted in Al-Ain, UAE, between April 2009 and September 2010. This is a case series retrospective study where patients attending the metabolic clinic at Tawam Hospital were recruited. Thirty patients and 26 parents were included.

Results: We present evidence in the UAE of 7 new mutations and 19 mutations that have previously been reported in other populations, all causing a number of common IEM disorders, including phenylketonuria, maple syrup urine disease, glycogen storage diseases, beta-ketothiolase deficiency, and Zellweger syndrome among many others.

Conclusions: Reflecting the diverse ethnic groups residing in the UAE, we found mutations in several different population groups. However, consanguinity is evident in most cases. This report is of utmost importance for taking the necessary steps toward the prevention of inherited disorders, not just in the UAE, but anywhere in the world where these Arab and Asian populations reside, or where consanguinity is a cultural norm.

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Inborn errors of metabolism (IEM) are a group of inherited, mostly autosomal recessive disorders that encompass several branches of intermediate biochemical and metabolic pathways in the body. These pathways include amino acid metabolism, fatty acid oxidation, pyruvate and carbohydrate metabolism, as well as organellar disorders such as lysosmal storage disease and peroxisomal disorders. Due to their mode of inheritance, IEM disorders are generally more common in highly consanguineous populations, including those of the UAE and most Arab countries.[1] Many of these disorders carry serious clinical consequences to the affected neonates or young infants, which include mild to severe irreversible mental retardation, physical handicaps or even early death. In most cases, early detection and appropriate management reduce or can even eliminate the complications associated with many of those disorders, and many countries have therefore developed national neonatal screening programs,[2] allowing diagnosis and the possibility of intervention. Reports from the Arabian Gulf region indicate that metabolic diseases constitute a significant cause of neonatal and infant death and mental retardation. Using tandem mass spectroscopy (TMS), Afifi and Abdul-Jabbar[3] screened newborns for 15 common metabolic diseases in the Saudi Arabian population, and estimated the metabolic disease ratio for the Saudi population as 1:1000 per year (defined as the ratio of newborns diagnosed with IEM to the total newborn population in one year). This rate is higher than that of the USA (1:4000), Japan (1:7000), and many other developed countries.[3] Furthermore, hospital based studies in the Sultanate of Oman, a country that is ethnically and geographically close to the UAE, indicated a relatively high prevalence of IEM disorders.[4,5] Joshi and Venugopalan[5] found that the most common IEMs in Oman were maple syrup urine disease (MSUD), propionic acidemia, urea cycle defects, and isovaleric acidemia. The authors reported that consanguinity and a positive family history were evident in most cases. It therefore follows that the prevalence of this group of genetic disorders in the UAE is high; however, this has not been well documented or studied at the molecular level. A retrospective study of IEMs at Al-Wasl Hospital in Dubai conducted by the Centre for Arab Genomic Studies Work Group between 1995 and 2004, and an internal audit by Al-Wasl Hospital, indicated the presence of at least 30 metabolic disorders in the UAE population.[6] These included several IEMs found in Oman, such as phenylketonuria (PKU), homocystinuria, propionicacidemia, MSUD, Krabbe disease, and galactosemia.[7] It was evident from this survey that most common metabolic disorder in the UAE is PKU, with an incidence of approximately 1:14000 since it was included in the national newborn screening program in 1995.[8] The molecular basis of most IEM disorders is not well defined for the UAE population, which is currently made up of local Emirati population groups and numerous immigrant population groups mostly from nearby India, Pakistan and other, genetically diverse, Arab countries. We recently elucidated the molecular basis of 2 metabolic disorders from the UAE. Abdulrazzaq et al[9] screened 2981 school-aged children for urine homogentisic acid level and identified a family with high levels of this metabolite, indicating alkaptonuria. Molecular studies in this family revealed a homozygous single nucleotide deletion in exon 3 (c.174delA) leading to a frameshift at amino acid position 58 (p.R58fs). In a second study, we identified a homozygous single nucleotide deletion in the *ARG1* gene in 3 affected siblings of Pakistani origin with arginase deficiency.[10] In this study, we report the mutational analysis of patients residing in the UAE and affected by a spectrum of IEM disorders. Some of these mutations are new records; others are newly recorded in this region. The importance of these mutations is in their strength as diagnostic tools for IEMs, providing the population with more accurate indications and therefore allowing intervention at an early enough stage that might prevent infant morbidity and mortality.

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Methods. The subjects described in this study were diagnosed and managed by clinicians at Tawam Hospital, Al-Ain, UAE. The medical records were examined, and the molecular genetics diagnostic reports were used to compile the data presented in this article. This project was approved by the Al-Ain Medical Human Research Ethics Committee-protocol number 10/09. The study was conducted in the city of Al-Ain, UAE, between April 2009 to September 2010. A total of 30 patients and 26 parents were recruited and studied.

The molecular testing of subjects suspected of having metabolic disorders was carried out by certified diagnostic laboratories, or at the Molecular Genetics Laboratory of the Faculty of Medicine and Health Sciences, UAE University. Only advanced genetic studies were carried out at the research institutes outside the UAE. Phenylketonuria (PKU): *PAH* gene sequencing was carried out at the University Children's Hospital Zurich, Switzerland. Alpha-Methylacetoacetic Aciduria (beta ketothiolase): *ACAT1* gene sequencing was

carried out at Centogene, Schillingallee 68, Germany. Maple Syrup Urine Disease (MSUD): *BCKDHB* gene sequencing and gene deletion/duplication studies were carried out at Emory University School of Medicine, USA. Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD): *ACADM* gene sequencing was carried out at Sheffield Molecular Genetics Services, Sheffield Children NHS Foundation Trust, UK. Hereditary Fructose Intolerance: *ALDOB* gene sequencing was carried out at Emma Children Hospital AMC, University of Amsterdam, The Netherlands. Fructose-1,6-bisphosphatase Deficiency: *FBP1* gene sequencing was carried out at Sheffield Molecular Genetics Services, Sheffield Children NHS Foundation Trust, UK. Zellweger Syndrome: *PEX6* gene sequencing was carried out at Emma Children Hospital AMC, University of Amsterdam, The Netherlands. Glycogen Storage Disease type 1A: *G6PC* gene sequencing was carried out at the Great Ormond Street Hospital for Children NHS Trust, UK. Glycogen Storage Disease type 2 (Pompe Disease): *GAA* gene sequencing was carried out at the Department of Clinical Genetics, Erasmus MC, Univeritair, Medich Centrum Rotterdam, the Netherlands. I-Cell Disease: *GNPTAB* gene sequencing was carried out at the Centogene Institute of Molecular Diagnostics, Germany. Sandhoff Disease: *HEXB* gene sequencing was carried out at Molecular Genetics Laboratory, Emory University School of Medicine, USA. Crigler-Najjar Syndrome: *UGT1* gene sequencing was carried out at Molecular Genetics Laboratory, Ninewells Hospital and Medical School, University of Dundee, UK. Citrullinemia type 1: *ASS1* gene sequencing was carried out at the Universitasklinikum, Munster, Germany. GM1-Gangliosidosis, Type I: *GLB1* gene sequencing was carried out at the Faculty of Medicine and Health Sciences Molecular Genetics Laboratories, UAE University, UAE.

Since this is a case series descriptive study based on relatively small number of patients reporting mutations in their DNA, there was no need to use any statistical analysis.

Results. We found numerous mutations from several important IEM diseases. These need to be exposed and documented in order for them to be incorporated into newborn screening programs or other diagnostic services.

Amino acid metabolism disorders. a) *Phenylketoneuria (PKU).* **Table 1** summarizes the mutations observed among PKU patients in the UAE. Six of these mutations have been reported in European populations, and one in a Chinese patient. This is the first record of these mutations in the UAE.

b) Canavan disease. We found a homozygous mutation c.914C>A (p.A305E) in the *ASPA* gene (**Table 1**). A number of mutations have been reported in patients from Saudi Arabia indicating heterogeneity of this condition among Arab patients.[11]

c) Maple syrup urine disease (MSUD). We reported a novel homozygous mutation in the *BCKDHB* gene from a Pakistani patient (**Table 1**). The deletion of exons 9 and 10 causes a definite structural change of the protein and therefore impairs its activity.

d) Propionic acidemia. A homozygous nonsense mutation (p.E331X) in the *PCCB* gene in an Emirati patient of Omani origin has been identified (**Table 1**). This mutation has been previously reported in patients from Europe and North America.[12,13]

e) Citrullinaemia. We identified a recurring missense mutation (c.349G>A; p.G117S) in the *ASS1* gene (**Table 1**) from patients of Pakistani origin. Previous reports of mutations in this gene have come from many diverse populations, and the previous report of this mutation came from a Turkish patient.[14]

Carbohydrate, energy and fatty acid metabolic disorders. *a) Glycogen Storage Disease Type 1A.* A mutation in the *G6PC2* gene (c.59A>G; p.Q20R) was found in an Emirati patient (**Table 2**). This mutation has been reported previously in a German and Tunisian patients.[15,16]

b) Hereditary fructose intolerance. A recurrent mutation (c.524C>A; p.A175D) in the *ALDOB* gene of a patient from a consanguineous Jordanian family was identified (**Table 2**). The parents were heterozygous for the mutation.

c) Fructrose-1,6-Diphosphatase deficiency. We described a 4 nucleotide deletion (c.616_619delAAAG) in the *FBP1* gene from an Emirati patient (**Table 2**) whose parents were both carriers. This mutation was previously reported in a German patient,[17] the deletion leads to a frame shift at position 206 (p.K206fs), causing loss of expression and therefore of enzyme activity.

d) ß-Ketothiolase deficiency. Two novel heterozygous mutations (c.460G>A + c.578T>G; p.E154K + p.M193R) were identified in the *ACAT1* gene of an Indian patient (**Table 2**) whose parents are carriers of these mutations. E154K constitutes the replacement of an acidic residue (glutamic acid) with a basic (lysine) residue, and M193R substitutes a small nonpolar residue (methionine) with a much larger basic residue (arginine). Both mutations are in a highly conserved functional domain of the protein, and both were predicted by PolyPhen[18] to be probably damaging to protein structure.

e) Medium Chain Acyl-CoA Dehydrogenase. In a Palestinian child whose parents were both carriers,

Table 1 - Mutations identified in amino acid metabolic disorders in the United Arab Emirates population.

Disorder	Gene details	Nucleotide change	Protein change	National origin	Reference
Phenylketonuria (PKU) (MIM 261600)	*PAH* NM_000277.1 MIM* 612349	c.165delT	F55Lfs	Syrian	Present study
		c.168+5G>C (IVS2+5G>C)	Splice	UAE	Present study
		c.727C>T	R243X	Pakistan	Present study
		c.728G>A	R243Q	Pakistan	Present study
		c.755G>A	R252Q	UAE	Present study
		c.782 G>A	R261Q	UAE	Present study
		c.1066-11G>A	Splice	UAE	Present study
Canavan disease (MIM 271900)	*ASPA* NM_000049.2 MIM 608034	c.914C>A	A305E	NA	Present study
Alkaptonuria (MIM 203500)	*HGD* NM_000187.2 MIM 607474	c.174delA (c.342delA)	R58 fs	UAE	9
Maple Syrup Urine Disease (MSUD) (MIM 248600)	*BCKDHB* NM_183050.1 MIM 284611	del exons 9 & 10	-	Pakistan	Present study
Propionic Acidemia (MIM 606054)	*PCCB* NM_000532.3 MIM 232050	c.991dupT	E331X	Oman	Present study
Citrullinaemia, classic (MIM 215700)	*ASS1* NM_000050.4 MIM 603470	c.349G>A	G117S	Pakistan	Present study
Argininemia (arginase deficiency) (MIM 207800)	*ARG1* NM_000045.2 MIM 608313	c.93delG	L31 fs	Pakistan	10

PAH - phenylalanine hydroxylase, *ASPA* - Aspartoacylase, *HGD* - homogentisate 1,2 dioxygenase, *BCKDHB* - branched-chain keto acid dehydrogenase-1, beta polypeptide, *PCCB* - propionyl-coa carboxylase, beta subunit, *ASS1* - argininosuccinate synthetase-1, *ARG1* - arginase, NA - not available

Table 2 - Mutations identified in carbohydrate and mitochondrial energy metabolic disorders in the United Arab Emirates population.

Disorder	Gene details	Nucleotide change	Protein change	National origin	Reference
Disorders of carbohydrate metabolism					
Glycogen storage disease type-1A (MIM 232200)	*G6PC2* NM 000151.2 MIM 608058	c.59A>G	Q20R	UAE	Present study
Hereditary fructose intolerance (MIM 229600)	*ALDOB* NM_000035.3 MIM* 612724	c.524C>A	A175D	Jordan	Present study
Fructose-1,6-bisphosphate deficiency (MIM 229700)	*FBP1* NM_000507.2 MIM 611570	c.616_619delAAAG	K206fs	UAE	Present study
Disorders of mitochondrial energy metabolism					
ß-Ketothiolase deficiency (MIM 203750)	*ACAT1* NM 000019.3 MIM 607809	c.460G>A/c.578T>G (compound heterozygousity)	E154K M193R	India	Present study
Medium chain acyl-CoA dehydrogenase deficiency (MCADD) (MIM 201450)	*ACADM* NM_000016.4 MIM 607008	c.431_434delAGTA	K144fs	Palestine	Present study

G6PC2 - glucose-6-phosphatase, catalytic-2, *ALDOB* - aldolase-b, fructose-bisphosphate, *FBP1* - fructose-1,6-bisphosphatase-1, *ACAT1* - acetyl-coa acetyltransferase-1, *ACADM* - acyl-CoA dehydrogenase medium-chain

Table 3. Mutations identified in lysosomal storage disorders and other inborn errors of metabolism conditions in the United Arab Emirates population.

Disorder	Gene details	Nucleotide change	Protein change	National origin	Reference
Glycogen storage disease type II (GSDII, Pompe disease) (MIM 232300)	*GAA* NM_000152.3 MIM 606800	c.340_341insT c.1327-2A>G	K114fs Splice	Palestine UAE	Present study 20
I-Cell disease (mucolipidosis type II) (MIM 252500)	*GNPTAB* NM_024312.3 MIM 607840	c.3503_3504delTC	L1168fs	UAE	Present study
Sandhoff disease (MIM 268800)	*HEXB* NM_000521.3 MIM 606873	c.850C>T	R284X	Pakistan	Present study
GM1-gangliosidosis, type I (MIM 230500)	*GLB1* NM_000404.2 MIM 611458	c.1465_1466delAT c.451G>T c.914+4A>G	I489fs D151Y Splice	India UAE UAE	Present study 25 25
Peroxisomal disorders					
Zellweger syndrome (MIM 214100)	*PEX6* NM_000287.3 MIM 601498	c.611C>G	S204X	UAE	Present study
Disorders of bilirubin metabolism					
Crigler-Najjar II (MIM 606785)	*UGT1A1* NM 000463.2 MIM 191740	c.993A>G (1073A>G)	Q331R	UAE	Present study

GAA - glucosidase, alpha, acid, *GNPTAB* - n-acetylglucosamine-1-phosphotransferase, alpha/beta subunits, *HEXB* - hexosaminidase-b, *GLB1* - galactosidase, beta-1, *PEX6* - peroxisome biogenesis factor 6, *UGT1A1* - udp-glycosyltransferase-1 family, polypeptide a1

we found a small homozygous deletion (c.431_434delAGTA; p.K144fs) in the *ACADM* gene (**Table 2**). Previous reports of this mutation were Korean and Japanese patients.[19]

Lysosomal storage disorders. a) *Glycogen Storage Disease Type II (Pompe Disease).* We recently reported 2 mutations in the *GAA* gene causing this disease in 3 Emirati infants from different families.[20] In this article, we reported a third infant from Middle Eastern background with a homozygous mutation (c.340_341insT) in *GAA* leading to a frame shift in exon 2 (**Table 3**). This mutation has previously been reported from the Middle East,[21] and in all cases the parents were carriers, and were first cousins.

b) I-cell disease. We reported the identification of a recurrent mutation (c.3503_3504delTC; p.L1168fs) in the *GNPTAB* gene in a family from UAE (**Table 3**). This mutation has been found in numerous patients from different ethnic backgrounds.[22,23]

c) Sandhoff disease. A homozygous mutation (c.850C>T; p.R284X) in the *HEXB* gene was found in a patient of Pakistani origin (**Table 3**). This mutation has been previously reported in an Italian patient.[24]

d) GM1-gangliosidosis type I. We reported a novel dinucleotide deletion (c.1465_1466delAT) in the *GLB1* gene in an Indian patient residing in the UAE (**Table 3**). There have been reports of other mutations in this gene from Emirati patients.[25]

Other IEM conditions. *a) Zellweger syndrome.* A novel mutation (c.611C>G; p.S204X) has been identified in the *PEX6* gene in an Emirati family.

b) Crigler-Najjar syndrome. We found a mutation in *UGT1A1* (c.993A>G; previously known as c.1073A>G; p.Q331R). Several mutations have been found in Tunisian population.[26]

Discussion. The national Emirati inhabitants of the UAE are ethnically diverse with ancestries from the north and south of the Arabian Peninsula, Persia, Baluchistan and East Africa. However, the majority of the current 5 million inhabitants are expatriates from the Asian subcontinent, Middle Eastern, African and European countries. Despite this mixture of populations, intermarriages between the groups are rare, with consanguineous marriages within the local Emirati, and within other Arab populations still the norm. This has lead to the formation of population isolates, and indeed the appearance of cases of recessive conditions such as IEM disorders.[1,27,28] The UAE is currently ranked 6th out of 193 countries in terms of prevalence of birth defects,[29] with more than 270 genetic disorders reported in the national population. Similar to other populations in the region, the UAE has a high frequency of blood disorders, including beta and alpha thalassemia, sickle cell disease and glucose-6-phosphate dehydrogenase (G6PD) deficiency. Other genetic disorders are also

relatively common in the UAE, including cystic fibrosis, deafness, Joubert syndrome, and Meckel syndrome.[1] It is clear therefore that the UAE, like many other Middle Eastern countries, is exposed to a heavy burden of single gene disorders, including IEM. The development of effective and accessible diagnostic and related genetic counseling services is crucial, and requires knowledge of the molecular basis of these conditions. Few studies have so far included details of the molecular characterization of IEM disorders in the UAE. In this article, we report the identification of the molecular causes underlying a significant number of IEMs found among the diverse residents of the United Arab Emirates.

The most common IEM disorder in UAE is PKU, with a relative incidence of approximately 1:14,000.[8] We found 7 mutations responsible for PKU in the UAE, all of which have been previously reported in other populations, but none of which are as yet incorporated into the national newborn screening program.[8] Furthermore, we have found several novel mutations that have not been reported previously, and others that are new records for Arab populations. Lysosomal storage diseases comprise more than 40 distinct conditions but collectively they affect one in 5000 individuals. In this article, we report the molecular causes of several lysosomal metabolic disorders including glycogen storage disease type II (Pompe Disease), I-Cell disease (Mucolipidosis type II), Sandhoff disease and GM1-Gangliosidosis type I. In most cases, the mutations we found were previously reported in other populations. However, the 3 mutations found in patients with GM1-Gangliosidosis type I (c.451G>T, c.914+4A>G and c.1465_1466delAT) seem to be novel; 2 of them are found in UAE patients[25] whereas the third was found in an Indian patient. All of these mutations may become valuable diagnostic tools for newborn screening and other diagnostic settings.[7]

The study limitations include the small sample size, but this is expected for case studies in rare metabolic conditions.

In conclusion, this article provides a valuable contribution to the diagnostic armory of healthcare providers in the Middle East. Reflecting the diverse ethnic groups residing in the UAE, we found mutations in several different population groups. This report is of utmost importance for taking the necessary steps toward the prevention of inherited disorders, not just in the UAE, but anywhere in the world where these Arab and Asian populations reside.

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