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CLINICAL & BASIC RESEARCH

Mutation Spectrum and Birth Prevalence of Inborn Errors of Metabolism among Emiratis

A study from Tawam Hospital Metabolic Center, United Arab Emirates

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الطفرات الوراثية و نسبة شيوع الأمراض الاستقلابية عند الإماراتيين

دراسة من مركز الأمراض الاستقلابية بمستشفى توام – الإمارات العربية المتحدة

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ABSTRACT: ***Objectives:*** This study aimed to determine the mutation spectrum and prevalence of inborn errors of metabolism (IEM) among Emiratis. ***Methods:*** The reported mutation spectrum included all patients who were diagnosed with IEM (excluding those with lysosomal storage diseases [LSD]) at Tawam Hospital Metabolic Center in Abu Dhabi, United Arab Emirates, between January 1995 and May 2013. Disease prevalence (per 100,000 live births) was estimated from data available for 1995–2011. ***Results:*** In 189 patients, 57 distinct IEM were diagnosed, of which 20 (35%) entities were previously reported LSD (65 patients with 39 mutations), with a birth prevalence of 26.87/100,000. This study investigated the remaining 37 (65%) patients with other IEM (124 patients with 62 mutations). Mutation analysis was performed on 108 (87%) of the 124 patients. Five patients with biotinidase deficiency had compound heterozygous mutations, and two siblings with lysinuric protein intolerance had two homozygous mutations. The remaining 103 (95%) patients had homozygous mutations. As of this study, 29 (47%) of the mutations have been reported only in Emiratis. Two mutations were found in three tribes (biotinidase deficiency [BTD, c.1330G>C] and phenylketonuria [PAH, c.168+5G>C]). Two mutations were found in two tribes (isovaleric aciduria [IVD, c.1184G>A] and propionic aciduria [PCCB, c.990dupT]). The remaining 58 (94%) mutations were each found in individual tribes. The prevalence was 48.37/100,000. The most prevalent diseases (2.2–4.9/100,000) were biotinidase deficiency; tyrosinemia type 1; phenylketonuria; propionic aciduria; glutaric aciduria type 1; glycogen storage disease type Ia, and mitochondrial deoxyribonucleic acid depletion. ***Conclusion:*** The IEM birth prevalence (LSD and non-LSD) was 75.24/100,000. These results justify implementing prevention programmes that incorporate genetic counselling and screening.

Keywords: Metabolism, Inborn Errors; Mutations; Prevalence; Founder Effect; United Arab Emirates.

الملخص: **الهدف**: هدفت الدراسة إلى تحديد مدى انتشار الأمراض الاستقلابية ومعرفة طفراتها الوراثية **الطريقة**: تضمنت تسجيل كل الطفرات الوارثية في جميع المرضى الذين تم تشخيصهم بالأمراض الاستقلابية (بعد استبعاد أمراض الاختزان في الجسيمات الحالة (أمراض التخزين الليسوسومية) في مركز الأمراض الاستقلابية بمستشفى توام – الإمارات العربية المتحدة خلال الفترة من يناير 1995 إلى مايو 2013 ومن ثم تم تقديرمعدل انتشار الأمراض الاستقلابية (لكل 100,000 مواليد أحياء) **النتائج**: تم تشخيص 57 مرضا من مختلف الأمراض الاستقلابية في 189 مريض منهم 20 (35%) من فئة أمراض الاختزان في الجسيمات الحالة (65 مريض لديهم 39 طفرة وراثية) بنسبة 26.87 لكل 100,000 .و السبعه والثلاثون مريضا الباقون (65%) هم موضع دراستنا الحالية (124 مريضا لديهم 62 طفرة وراثية). تم تحليل للطفرات في 108 من أصل 124 مريضا (87%) وجدت طفرات متخالفة الألائل المركبة في خمس مرضى لديهم عوز انزيم البيوتنيديز تم تحديد طفرتين زيجوت متماثلة الألائل في شقيقين لديهم مرض عدم التحمل لبروتين الليزين أما باقي المرضى 103 (95%) فوجدت لديهم طفرات زيجوت متماثلة الألائل. ومن الجدير بالذكر أن 29 (47%) طفرة وراثية تم حصرها في الإماراتيين فقط الى الآن. وجدت طفرتين في 3 قبائل فقط (عوز انزيم البيوتنيديز و بيلة الفينل كيتونبينما وجدت طفرتين في قبيلتين (احمضاض الدم الايزوفاليريكي و احمضاض الدم البروبيونيكي) ووجد 58 (94%) طفرة في عدد من القبائل الفردية بمعدل انتشار 48.37 لكل 100,000. وكانت أكثر الأمراض شيوعا (4.9 –2.2/100,000) كالآتي: عوز انزيم البيوتنيديز وفرط تيروزين الدم و بيلة الفينل كيتون و احمضاض الدم البروبيونيكي و بيلة حمض الغلوتاريك النوع الأول وداء اختزان الغليكوجين النوع الأول أ ونفاذ الحمض النووي الميتوكوندري **الخلاصة**: معدل انتشارالأمراض الاستقلابية في المواليد الإماراتيين (أمراض الاختزان في الجسيمات الحالة أو غيرها) يقدر بحوالي 100,000/75.24. هذه النتائج تبرر تنفيذ البرامج الوقائية التي تتضمن الاستشارة الوراثية والمسح الجيني عند الولادة.

مفتاح الكلمات: أمراض الاستقلاب في المواليد؛ الطفرات الجينية؛ معدل انتشار؛ تأثير مؤسس؛ الإمارات العربية المتحدة.

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Advances in Knowledge

- *The birth prevalence of inborn errors of metabolism (IEM) among Emiratis is 75.24 per 100,000 (1 per 1,329 live births).*
- *Of the 62 mutations identified in this study, 29 (47%) have so far been reported only in Emiratis.*
- *The most prevalent IEM in the United Arab Emirates (UAE) are biotinidase deficiency; tyrosinaemia type 1; phenylketonuria; propionic aciduria; glutaric aciduria type 1; glycogen storage disease type Ia, and mitochondrial deoxyribonucleic acid depletion.*

Application to Patient Care

- *The high prevalence of IEM in the UAE justifies implementing intensive prevention programmes that incorporate genetic counselling and screening.*
- *The prevention of IEM requires premarital and prenatal testing, as well as counselling.*
- *Early detection through newborn screening will improve patient outcomes, although prevention of these IEM is the ultimate goal.*
- *Prevention programmes will decrease the burden of IEM on the UAE's health system.*

Studies of the mutation spectrum and prevalence of IEM in the Middle East and North Africa (MENA) are still insufficient.[1] These disorders, which are usually autosomal recessive, are more frequent in the MENA region due to "founder mutations" and consanguinity.[2] The primary objective of this study was to provide data from the United Arab Emirates (UAE) that justify initiating prevention programmes, such as premarital screening and counselling. These data are also required to assess the impact of managing these patients within the UAE health systems.

The population of Emiratis is ethnically diverse, claiming ancestry from the Arabian Peninsula, Persia, Baluchistan and East Africa. Emirati society consists of at least 70 distinct tribes. Despite the ethnic diversity, inter-tribal marriages are much less common than intra-tribal ones.[3] In 2010, the UAE's population was estimated at 8,264,070; 87% of this population was expatriate.[4] In 2011, the total live birth in UAE was 83,950, of whom only 40% were Emiratis.[5]

The Center for Arab Genomic Studies reports 334 genetic diseases in the UAE, including IEM, congenital anomalies and mental retardation.[6] Moreover, the prevalence and mutation spectrum of LSD in the UAE was recently reported and compared with published data from Western countries.[7,9–11] This study was designed to report on other IEM entities among Emiratis.

Methods

This project was approved by the Al-Ain Medical Human Research Ethics Committee (protocol #12/59). The study's population did not include patients who had received treatment exclusively abroad as they represent an unknown number of patients, nor did the study include the 22 patients managed at the Latifa Hospital in Dubai.

For calculating the disease birth prevalence, all citizens of the UAE with IEM (excluding those with LSD) who were evaluated between January 1995 to December 2011 at Tawam Hospital, the only metabolic referral center in Abu Dhabi, were included. The mutation spectrum for non-LSD IEM included all patients evaluated from January 1995 to May 2013.

The diagnosis of IEM was based on the clinical findings and screening tests, and was confirmed by biochemical and/or genetic studies. In many patients, the diagnosis was also supported by family studies.

Direct genomic sequencing and multiplex ligation-dependent probe amplification (MLPA) studies for deletion/duplication mutations of IEM genes were performed by accredited genetic diagnostic laboratories. Novel variants were verified by extended family genetic testing as well as damage-prediction assessment using three different prediction tools: SIFT (Sorting Intolerant From Tolerant),[12] PolyPhen-2 (Polymorphism Phenotyping Version 2)[13] and MutationTaster.[14]

The estimated birth prevalence of each disease was calculated as the number of patients with a specific disease divided by the total number of Emirati live births in the UAE during the birth period (the time interval between the year of birth of the oldest patient and the year of birth of the youngest patient).[10] The birth prevalence of a single patient was calculated as one divided by the number of total Emirati live births in the UAE between 1995 and 2011.[11] The affected deceased siblings and fetuses that had not been evaluated at the Metabolic Center were not included in this study. The number

of live births per year was obtained from the UAE National Bureau of Statistics but data were available only up to 2011.[4] However, the mutation spectrum of patients who were diagnosed after 2011 was also included.

Results

Excluding those with LSD, 37 distinct IEM were diagnosed in the 124 patients between January 1995 and May 2013. Mutation analysis was performed on 108 (87%) patients. In 43 tribes, 62 mutations were found, with most of the reported mutations being homozygous.

Five patients with biotinidase deficiency had compound heterozygous mutations, and two siblings with lysinuric protein intolerance had two homozygous mutations. The remaining 103 (95%) patients had homozygous mutations. As of the date of this study, 29 (47%) of the mutations had been reported only in Emiratis [Table 1].

Biotinidase deficiency (*BTD*, c.1330G>C) and phenylketonuria (PKU) (*PAH*, c.168+5G>C) occurred in three separate tribes. Isovaleric aciduria (*IVD*, c.1184G>A) and propionic aciduria (*PCCB*, c.990dupT) occurred in two separate tribes. The two tribes with propionic aciduria were originally from Oman. The remaining 58 (94%) mutations occurred in individual tribes [Table 1]. The 29 mutations unique to the UAE point to a "founder effect".

Diseases with a prevalence of 2.2–4.9 per 100,000 live births were biotinidase deficiency; tyrosinaemia type 1; PKU; propionic aciduria; glutaric aciduria type 1; glycogen storage disease type Ia; mitochondrial deoxyribonucleic acid (DNA) depletion; melanocortin 4 receptor deficiency, and chloride diarrhoea [Table 1].

Diseases with a prevalence of 1.1–1.9 per 100,000 live births were isovaleric aciduria; fructose 1,6-bisphosphatase deficiency; glutaric aciduria type II; lipoamide dehydrogenase deficiency; alpha-methylacyl-CoA racemase, and neonatal diabetes [Table 1].

Diseases with a prevalence of ≤0.98 per 100,000 live births were alkaptonuria; sulfite oxidase deficiency; nonketotic hyperglycinaemia; maple syrup urine disease; 3-methylcrotonylglycinuria; carbamoyl phosphate synthetase deficiency; citrullinaemia type 1; argininosuccinate lyase deficiency; lysinuric protein intolerance; cobalamin B deficiency; cobalamin C deficiency; pyridoxine-dependent seizures; medium-chain acyl-CoA dehydrogenase deficiency; carnitine deficiency; 3-ketothiolase deficiency; lipoamide dehyrogenase deficiency; adrenoleukodystrophy; Zellweger syndrome; bile acid disorder; progressive familial intrahepatic cholestasis; Crigler-Najjar syndrome; osteopetrosis, and butyrylcholinesterase deficiency [Table 1].

Discussion

The UAE has a very high net migration rate, making it challenging to estimate the birth prevalence of a disease as a ratio of the entire population, so this study only estimated the birth prevalence of IEM among Emiratis.[5]

Intra-tribal marriages are dominant in the UAE, occurring in over 50% of unions. First-cousin marriages account for about 30% of those cases.[3] The mutation spectrum and birth prevalence of LSD among Emiratis has recently been reported, focusing on other IEMs in the same population [Table 1].[6,7] The main purpose of this study was to provide data that justify implementing prevention programmes, such as prenatal and premarital screening and counselling. The results show a birth prevalence for non-LSD IEM of 48.37 per 100,000 (1:2,067 live births) [Table 1], giving an overall IEM birth prevalence (LSD and non-LSD) of 75.24 per 100,000 (1:1,329 live births).[7] This level of occurrence justifies the need for intensive prevention programmes. The data also point to the need for prenatal and premarital genetic testing and counselling.

The overall disease prevalence of IEM in British Columbia, Canada, (1969–1996) is about 40 patients per 100,000 live births (1:2,500 live births); the prevalence in Italy (1985–1997) is 1:3,707 live births.[15,16] The prevalence of classical IEM of amino acids, organic acids and fatty acid oxidation in Hong Kong is 1:4,122 live births.[17]

In our study, 62 distinct mutations were identified [Table 1]. Most mutations (95%) were homozygous, and 19 mutations were novel, not having been reported previously. As mentioned earlier, 29 (47%) have so far only been reported in Emiratis [Table 1].

The Centre for Arab Genomic Studies (CAGS)

Table 1: Disorder, estimated prevalence, gene and mutation spectrum of non-lysomal storage disorders inborn errors of metabolism in the United Arab Emirates

IEM	OMIM#	Genes/ RefSeq	Mutations
PKU†	261600	*PAH* NM_000277.1 n = 17	c.168+5G>C (splicing mutation)††; c.782G>A (p.R261G); c.970-2A>G**; c.1066-11G>A; c.755G>A** (p.R252Q)**
Alkaptonuria§	203500	*HGD* NM_000187.2 n = 1	c.174delA (p.R58fs)
Tyrosinaemia type I†	276700	*FAH* NM_000137.2 n = 2	**c.1156G>C (p.D386H);** c.1A>G (p.M1V)
Sulfite oxidase deficiency§	606887	*SUOX* NM_000456.2 n = 1	c.650G>A (p.217R>Q)
Nonketotic hyperglycinaemia§	238300	*GLDC* NM_000170.2 n = 1	**c.919G>T (p.E307*)**
Maple syrup urine disease§	248600	*DBT* NM_001918.2 n = 1	**c.1281+1 G>T**
Propionic aciduria†	606054	*PCCA* NM_000282.3 n = 2	**c.1598_1601delTTGT (p.F533Wfs*5)**
		PCCB NM_000532.3 n = 3	**c.1142G>A (p.C381Y);** c.990dupT (p.E331*)‡‡
3-methylcrotonyl glycinuria§	210200	*MCCC1* NM_020166.2 n = 3	**c.89+2_89+34del; c.1106C>G (p.P369R)**; c.694C>T (p.R232W)
		MCCC2 NM_022132.3 n = 1	**c.735dupC (p.V247Gfs*2)**
Isovaleric aciduria‡	243500	*IVD* NM_002225.3 n = 9	**c.1193G>A (p.R398Q);** c.295+5G>A; c.1175G>A (p.R392H); c.1184G>A**‡‡ (p.R395Q)**; c.1136_1138+4delTTGGTGA (p.F382fs)**
Glutaric aciduria type I†	231670	*GCDH* NM_000159.2 n = 5	**c.242C>T (p.P81L); c.427G>A (p.V143I);** c.1204C>T (p.R402W)
Carbamoyl phosphate synthetase deficiency§	237300	*CPS1* NM_001875.2 n = 1	c.1590dup (p.V531CfsX91)**
Citrullinaemia type 1§	603470	*ASS1* NM_000050.4 n = 2	c.535T>C (p.W179R)
Argininosuccinate lyase deficiency§	207900	*ASL* NM_001024943.1 n = 1	**c.332G>A (p.R111Q)**
Lysinuric protein intolerance§	222700	*SLC7A7* NM_001126105.2 n = 4	c.499+1G>C**; **c.999G>C¶ (p.R333S); c.1005C>A¶ (p.F335L)**

Biotinidase deficiency†	253260	*BTD* NM_000060.3 n = 7	c.1330G>C (p.D444H)††; c.1207T>G (p.F403V); c.968A>G (p.H323R); c.1489C>T (p.P497S); c.557G>A (p.C186Y)
Cobalamin B deficiency§	251110	*MMAB* NM_052845.4 n = 1	c.197-1 G>T (intronic)
Cobalamin C deficiency§	277400	*MMACHC* NM_015506.2 n = 1	c.271insA (p.R91KfsX14)
Pyridoxine-dependent seizures§	266100	*ALDH7A1* NM_001182.4 n = 1	**deletion of exon 7**
Fructose-1, 6-bisphosphatase deficiency‡	611570	*FBP1* NM_000507.2 n = 2	c.616_619delAAAG (p.K206fs*70)**
Glycogen storage disease type Ia†	232200	*G6PC* NM_000151.2 n = 2	c.59A>G (p.Q20R)
Glutaric aciduria type II‡	231680	*ETFDH* NM_004453.2 n = 4	**c.807A>C (p.Q269H)**
Medium-chain acyl-CoA dehydrogenase deficiency§	607008	*ACADM* NM_000016.2 n = 1	c.985A>G (p.K329E)
Carnitine deficiency§	212140	*SLC22A5* NM_003060.2 n = 1	c.248G>T (p.R83L)
3-ketothiolase deficiency§	607809	*ACAT1* NM_000019.3 n = 3	**c.86_87dupTG (p.E30Wfs*11); c.854C>T (p.T285I)**
Lipoamide dehyrogenase deficiency‡	238331	*DLD* NM_000108.3 n = 2	c.685G>T (p.G229C)
Mitochondrial DNA depletion†	203700	*POLG* NM_002693.2 n = 7	c.3286C>T (p.R1096C)
	251880	*DGUOK* NM_080916.1 n = 1	**c.427 T>C (p.S143P)**
	609560	*TK2* NM_004614.4 n = 2	c.173A>G (p.N58S)
Adrenoleukodystrophy§	300100	*ABCD1* NM_000033.3 n = 1	c.309C>G (p.S103R)
Zellweger syndrome§	614862	*PEX6* NM_000287.3 n = 1	c.611C>G (p.S204*)**
Alpha-methylacyl-Co A racemase‡	614307	*AMACR* NM_001167595.1 n = 3	c.877T>C (p.C293R)
Bile acid synthesis disorder§	235555	*AKR1D1* NM_005989.3 (n = 1)	c.781C>T (p.R261C)**

Progressive familial intrahepatic cholestasis§	601847	*ABCB11* NM_003742.2 n = 1	c.1897A>C (p.T633P)
Crigler-Najjar syndrome§	606785	*UGT-1* NM_000463.2 n = 1	c.1073A>G (p.N358S)**
Melanocortin 4 receptor deficiency†	601665	*MC4R* NM_005912.2 (n = 2)	c.485C>T (p.T162I)
Chloride diarrhoea†	214700	*SLC26A3* NM_000111.2 n = 3	c.559G>T (p.G187*)
Osteopetrosis§	259730	*CA2* NM_000067.2 n = 2	c.232+1G>A
Butyrylcholinesterase deficiency§	177400	*BCHE* NM_000111.2 n = 1	c.293A>G (p.D98G)
Neonatal diabetes mellitus‡	176730	*INS* NM_001185098.1 n = 3	c.-331C>G

IEM = inborn errors of metabolism; OMIM = Online Mendelian Inheritance in Man; RefSeq = National Center for Biotechnology Information Reference Sequence database; PKU = phenylketonuria; DNA = deoxyribonucleic acid.

*† Estimated birth prevalence of 2.2–4.9 per 100,000; ‡ Estimated birth prevalence of 1.1–1.9 per 100,000; § Estimated birth prevalence of <0.98 per 100,000; ¶ Both mutations found in the same patient in a homozygous state; ** Mutations reported so far only in Emiratis; †† The two mutations found in three separate tribes and ‡‡ the two mutations found in two separate tribes (the remaining mutations occurred in individual tribes);* ***Bold*** *= Novel mutations that have not previously been reported.*

has reported 29 published IEM in UAE (16 LSD and 13 other IEM). Only nine of the 13 non-LSD IEM entities are listed in Table 1. The remaining four disorders (argininaemia, mevalonic aciduria, homocystinuria and Menkes disease) occurred in the UAE, but data are lacking on whether these disorders exist in Emiratis or people of other nationalities. The 28 additional non-LSD IEM [Table 1] entities need to be included in the Catalogue of Transmission Genetics in Arabs database.[8]

Several IEM mutations in Middle Eastern populations have been reported.[6,18–21] In the case of isovaleric aciduria, three mutations (p.R392H, p.R395Q and p.F382fs) were reported in four unrelated Emirati families and one mutation (p.E408K) in an Egyptian family.[20] Alkaptonuria, due to the single nucleotide deletion of c.342delA (c.174delA), was reported in a family from Al Ain, UAE; the allelic prevalence was estimated at about 1%.[21]

In the UAE, screening began for PKU in 1995, for congenital hypothyroidism in 1998, sickle cell disease in 2002, congenital adrenal hyperplasia in 2005 and biotinidase deficiency in 2010.[22–24] The Expanded National Neonatal Screening Programme, implemented in 2011, covers over 90% of all neonates. It includes amino acid disorders (PKU, maple syrup disease, citrullinaemia type I and argininosuccinic aciduria); organic acid disorders (isovaleric aciduria; HMG-CoA lyase deficiency; beta-ketothiolase deficiency; glutaric aciduria type I; propionic aciduria, and methylmalonic aciduria) and fatty acid oxidation disorders (medium-chain acyl-CoA dehydrogenase deficiency). The registry for congenital anomalies and hereditary disorders, along with premarital genetic testing and counselling, were started in 1999.[23]

Biochemical studies can identify most IEM. The limitations to this approach, however, include the invasive sample collection (skin, liver or muscle biopsy), the limited availability of clinically accredited biochemical diagnostic laboratories and the need for relatively laborious analyses. Thus, the current clinical practice relies on combining biochemical and genetic studies.

Identifying a mutation confirms the diagnosis, allows screening for asymptomatic family members, supports pre-implantation genetic programmes and may influence patient management. For example,

PKU patients with c.168+5G>C, c.782G>A or c.970-2A>G typically respond to sapropterin, while patients with c.1066-11G>A or c.755G>A are unresponsive.[25] In our practice, only ~50% of patients with c.168+5G>C responded to sapropterin and none of the patients with c.782G>A or c.970-2A>G responded to this treatment.

As shown in Table 1, the most prevalent diseases in the UAE are biotinidase deficiency; tyrosinaemia (type 1); PKU; propionic aciduria; glutaric aciduria type 1; glycogen storage disease type Ia; mitochondrial DNA depletion; melanocortin 4 receptor deficiency and chloride diarrhoea. Of the seven patients with biotinidase deficiency, most had a partial deficiency. When mutation analysis was performed on six patients, only one had a homozygous mutation with partial enzyme deficiency, while the other five carried compound heterozygous mutations (all born to parents of different tribes). Six of the seven patients were diagnosed by newborn screening after 2012, reflecting a high carrier frequency. Two siblings with lysinuric protein intolerance had two different homozygous mutations [Table 1]. The remaining patients had homozygous mutations.

Ten novel missense mutations were reported in this study [Table 1], all in patients with clinical and/or biochemical findings consistent with the disease. Future studies are needed to explain the functional effects associated with each of these mutations.

Two mutations (involving biotinidase deficiency and PKU) each occurred in three separate tribes. Two mutations (involving isovaleric aciduria and propionic aciduria) each occurred in two separate tribes. The remaining 58 mutations (94%) each occurred in individual tribes [Table 1]. The need for effective premarital testing and counselling and prenatal/pre-implantation genetic diagnoses was highlighted by the 19 families with more than one affected child.

This study reports 62 mutations. The 19 novel mutations that had not been previously reported are identified in Table 1 in bold. The 10 mutations that have been previously reported only in Emiratis are denoted by double asterisks in Table 1.[17–20] The remaining 33 mutations are known mutations, which are available at the Human Gene Mutation Database.[26] Identifying mutations allows the screening of asymptomatic family members and also supports pre-implantation genetic programmes. In the future, incorporating mutation analysis into newborn screenings as a second-tier test will decrease the number of false-positive cases and facilitate early treatment. Nevertheless, disease prevention remains the ultimate goal.

This study has some limitations. First, the birth prevalence of IEM was estimated based only on patients who presented clinically or were referred by the National Newborn Screening Programme. Tawam Hospital is the UAE's only referral center for metabolic diseases, and the 22 Emirati patients referred to Latifa Hospital were not included in this study. Thus it is possible that some patients who may have IEMs were not included in this study.

Second, the UAE's expanded National Newborn Screening Programme only started in 2011 so the population that has been screened for newborn IEM is limited. Third, patients who were born in 2012 and 2013 were not included in the calculation of disease prevalences since the total live births for those years were not yet available at the time of writing. Therefore, the reported IEM birth prevalences in Table 1 should be considered as rough estimations.

Fourth, the IEM disorders in Table 1 were diagnosed primarily by biochemical studies, which is the gold-standard approach. The mutation analyses were done by an accredited laboratory and the novel missense variants were not investigated by functional assays, such as expression analyses. Preferably, chromosomes originating from Emirati tribes should be studied to verify whether the sequence variants represented polymorphisms *versus* disorders. Thus, the responsibility of some mutations for causing a disease may require future studies.

Conclusion

The estimated birth prevalence of IEM among Emiratis is 75.24 per 100,000 (1 per 1,329 live births). Distinct IEM (n = 57) and 101 mutations have been identified thus far. These data strongly point to the need for genetic counselling and screening. Identifying mutations unique to the UAE will allow for more effective pre-implantation genetic testing and premarital testing in order to prevent further cases from occurring within families. Early detection through newborn screening and treatment may prevent irreversible organ damage.

However, in spite of the possibility of treatment, the prevention of genetic diseases should remain the ultimate goal.

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