# Prevalence and Genetic Variability of Inborn Errors of Metabolism in Bahrain

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**Objective: To evaluate the prevalence and the pattern of inborn errors of metabolism (IEMs), mutation spectrum and outcome.**

**Design: A Retrospective Analysis.**

**Setting: Salmaniya Medical Complex, Bahrain.**

**Methods: A seventeen-year retrospective study of patients diagnosed with IEMs was performed. The following were documented: IEMs categories, age, sex, origin, and consanguinity. In addition, molecular genetic result and outcome were documented.**

**Result: One hundred eighty-eight patients with IEM were included in the study. One hundred seventy-seven (94.1%) were consanguineous. Ninety-three (49.5%) patients were identified to have small molecules disorders, while 95 (50.5%) were large molecules disorders. Mutation analysis was done on 124 (66%) patients, and novel mutations were detected in 72 (38.3%). The overall death rate was 41.5%.**

**Conclusion: The high rate of IEMs in Bahrain warrants the need for implementing a national neonatal screening program to evaluate the exact burden of these disorders to reduce mortality and morbidity by early management. The detection of molecular genetic mutations in our population will help a prevention program through preimplantation genetic diagnosis; in addition, the presence of a large number of novel mutations will invariably help identifying the genetic variability in this region.**

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Inborn errors of metabolism (IEMs) result from a lack of activity of one or more specific enzymes in a single pathway of intermediary metabolites. They are often inherited as autosomal recessive. Biochemical consequences include the accumulation of substances present in small amounts, the deficiency of critical intermediary products, the deficiency of specific final products and the noxious excess of products of alternative metabolic pathways[1].

The clinical consequences of IEMs are often severe, and they are an important cause of morbidity and mortality in pediatrics[2]. IEMs classified into small and large molecule disorders. Small molecule disorders include amino acids, organic acids, urea cycle, carbohydrate metabolism, cholesterol and metal transport defects. Large molecule disorders include glycogen storage diseases, sphingolipidosis, mucopolysaccharidosis, oligosaccharidosis, mitochondrial diseases and congenital disorders of glycosylation[3].

The diagnosis of IEMs is based on detecting abnormal metabolites in the blood, urine and cerebral spinal fluid, analysis of enzymes activity, and molecular genetic testing[1]. Tandem mass spectrometry (TMS) is a standard tool for diagnosis and neonatal screening for some IEMs[4]. The cumulative incidence of IEMs is 1 in 2500-5000 live births worldwide[5]. It may reach 1 in 800-2500 live births in our neighboring countries[6,7]. In Bahrain, the burden of these disorders through incidence or prevalence has not yet been reported.

The aim of this study is to evaluate the prevalence and the pattern of inborn errors of metabolism (IEMs), mutation spectrum and outcome.

## METHOD

The study was performed from January 2000 and December 2017. The following were documented: IEMs categories, age, sex, origin, and consanguinity. In addition, molecular genetic result and outcome were documented. The diagnosis of IEMs was based on clinical suspicion followed by biochemical investigations including analysis of ammonia, lactic acid, plasma/urine amino acids, acylcarnitine profile and urine organic acids. Very long chain fatty acids, urine mucopolysaccharide and oligosaccharide were assayed based

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on the index of suspicion. Confirmation of the diagnosis was achieved in most cases by biochemical metabolites, measuring enzyme activity and/or molecular genetic testing. In instances where the former did not yield results, the confirmation was done using whole exome sequencing (WES). The prevalence is measured per 100,000 of population and P-value is calculated using (SPSS version 23).

## RESULT

One hundred eighty-eight were diagnosed with IEMs. The age range was from one week to 56 years. The mean age was 8.056 years with a standard deviation of 9.180; 25 (13.3%) were >15 years. Male to female ratio was 1:1.04; 69.7% were Bahrainis with a consanguinity rate of 94.1%. The overall prevalence of cases per 100,000 was 15.95 (1:6269 populations). The cases were classified into three groups based on the year of diagnosis (2000-2005, 2006-2011, and 2012-2017) and their exact prevalence was calculated accordingly, see table 1.

**Table 1: Prevalence (per 100000) in the Period 2000-2017 in Relation to Origin**

| | Bahraini | | | Non-Bahraini | | | Total | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases | Population | Prevalence | Cases | Population | Prevalence | Cases | Population | Prevalence |
| **2000-2005** | 28 | 445634 | 6.28 | 8 | 318888 | 2.51 | 36 | 764519 | 4.71 |
| **2006-2011** | 30 | 549799 | 5.46 | 11 | 591157 | 1.86 | 41 | 1140956 | 3.59 |
| **2012-2017** | 73 | 639290 | 11.42 | 38 | 703153 | 5.40 | 111 | 1342442 | 8.27 |
| **Total** | **131** | **558011** | **23.48** | **57** | **620404** | **9.19** | **188** | **1178415** | **15.95** |

Ninety-three (49.5%) patients were identified to have small molecule disorders, while 95 (50.5%) were large molecule disorders. Eighty-five patients (45.2%) were diagnosed at less than one year of age, 95 (50.5%) were small molecule disorders. Amino acids and organic acids disorders were the most common among the two categories of diseases with a total of 74 (39.4%) patients. Methylmalonic acidemia was the commonest disorder, 12 (6.4%) patients, followed by 3-hydroxyisobutyryl-CoA hydrolase (HIBCH), 8 (4.3%). Lysosomal storage diseases (LSD) were the second most common group of disorders comprising of 38 (20.2%) patients. Mucopolysaccharidosis were the most common LSD disorders, 13 (6.9%) patients. Respiratory chain disorders were detected in 35 (18.6%). Glycogen storage disease (GSD) type II was the most common subtype of GSDs, diagnosed in 10 patients among 19 patients diagnosed with different GSDs. Fatty acids oxidation defect (FAOD) were diagnosed in 12 patients (6.4%). The most prevalent type of FAOD was carnitine palmitoyltransferase-I deficiency 5 (2.7%), see table 2.

Mutation assay was performed for 124 (65.9%) patients, novel mutations were detected in 72 (38.3%) and all of them match the clinical picture of the disease and their biochemical markers, no significant difference (P-value = 0.6), see table 3.

The overall death rate was 41.5% with a mean age of 4.3 years. There was a highly significant relationship between disease classification and outcome (P-value < 0.01). A finding was revealed between death rate and novel mutation (P-value of 0.043). There was no significant change in death rate among the year of diagnosis (P-value 0.185).

**Table 2: Patients with Small and Large Molecule Disorders of IEMs Bahrain (2000-2017). Total Number of Patients (188)**

| Disease Groups | Disease category | Disease | Number of patients | % |
|---|---|---|---|---|
| Small Molecule Disorders | **Amino acids and organic acids** | | **74** | **39.4%** |
| | Methylmalonic acidemia | | 12 | |
| | Propionic acidemia | | 7 | |
| | Isovaleric acidemia | | 2 | |
| | Lysinuric protein intolerance | | 4 | |
| | Phenylketonuria | | 6 | |
| | MSUD | | 9 | |
| | Tyrosinemia | | 5 | |
| | Urea cycle defect | | 7 | |
| | HIBCH | | 8 | |
| | Others | | 14 | |
| | **Fatty acid oxidation defects** | | 12 | 6.4% |
| | VLCAD | | 4 | |
| | CPT I | | 5 | |
| | CPT II | | 2 | |
| | Primary carnitine deficiency | | 1 | |
| | **Porphyria** | | 6 | 3.2% |
| | **Pyridoxine-dependent seizures** | | 1 | 0.5% |
| | Total of SM | | 93 | |
| Large Molecule Disorders | **Lysosomal storage disease** | | 38 | 20.2% |
| | MPS II | | 2 | |
| | MPS III | | 8 | |
| | MPS IV | | 2 | |
| | MPS VI | | 1 | |
| | GM1 Gangliosidosis | | 5 | |
| | Galactosialidosis | | 7 | |
| | Tay Sachs | | 3 | |
| | Fucosidosis | | 2 | |
| | Niemann Pick AB | | 3 | |
| | Niemann Pick C | | 1 | |
| | Mucolipidosis II | | 3 | |
| | Fabry disease | | 1 | |
| | **Glycogen storage disease** | | 19 | 10.1% |
| | GSD I | | 4 | |
| | GSD II | | 10 | |
| | GSD III | | 5 | |
| | **Respiratory chain disorders** | | 35 | 18.6% |
| | **Peroxisomal** | | 2 | 1.1% |
| | **Neuronal ceroid lipofuscinosis** | | 1 | 0.5% |
| | Total of LM | | 95 | |
| **Total** | | | **188** | |

## DISCUSSION

Our findings revealed an overall prevalence of 15.95 per 100,000 (1:6269) populations. The prevalence rate identified is high for conditions that are considered rare internationally, as this figure is comparable to a common disease in Bahrain. Type I diabetes mellitus prevalence in Bahrain reported being 20 per 100,000 populations[9]. Our findings could not be compared with those reported in neighboring countries including Saudi Arabia and United Arab Emirate (UAE) as their results were shown as incidence rate. However, their findings were high compared to Western countries (Saudi Arabia reported 1:1381, UAE reported 1:1787, while British Columbia reported 1:2500 live birth)[5,7,10].

**Table 3: Molecular Genetic Variabilities among IEMs Patients of Small and Large Molecules Disorders (2000-2017)**

| Disease Category | Disease | Number of Patients | Gene | Reported Mutation | Novel Mutation |
|---|---|---|---|---|---|
| amino acids and organic acids | MMA | 1 | *MUT* | Homozygous mutation c.2179C>T (p.Arg727*) | |
| | MMA | 1 | *MUT* | | Homozygous mutation c.1975C>T (p.Gln659Ter) |
| | MMA | 1 | *MMAB* | Heterozygous mutation c.197-1 G>T | Heterozygous mutation c.577G>C (p.Glu193Gln) |
| | MMA | 2 | *MMAB* | Homozygous mutation c.557G>a (p.ARG186Gln) | |
| | MMA | 3 | *MMAB* | Heterozygous mutation c.197-1 G>T And heterozygous mutation c.562 G>A (p.Val188Met) | |
| | propionic acidemia | 1 | *PCCB* | Homozygous mutation c.[990dupT];[(990DUPT)], p.[(Glu331*)];[(Glu331*)] | |
| | propionic acidemia | 3 | *PCCB* | | Homozygous mutation c.[395_408del];[(395_408del)], p.[(serl 132Thrfs*24)];[(ser132Thrfs*24)] |
| | LPI | 3 | *SLC7A7* | | Homozygous mutation c.1429+1G>C (IVS9+1G>C) |
| | LPI | 1 | *SLC7A7* | | Homozygous mutation c.168T>G (p.Phe56Leu) |
| | PKU | 1 | *PAH* | Homozygous mutation c.691T>C, (p.S231P) | |
| | MSUD | 1 | *BCKDHB* | Homozygous mutation c.[853C>T];[(853C<T)], p.[(Arg285*)];[(Arg285*)] | |
| | MSUD | 1 | *BCKDHA* | | Homozygous mutation c.661_664delTACG (p.Tyr221Glnfs*108) |
| | tyrosinemia type 1 | 2 | *FAH* | | homozygous mutation c.791delT(p. Val264Glyfs*40) |
| | tyrosinemia type 1 | 1 | *FAH* | | Homozygous mutation c.710G>A (p.Arg237Gin) |
| | tyrosinemia type 1 | 1 | *FAH* | Heterozygous mutation c.374C>A(p. Thr125Lys) | Heterozygous mutation c.106+5G>A |
| | OTC | 2 | *OTC* | Hemizygous mutation c.912G>T(p. Leu304Phe) | |
| | CPS1 | 1 | *CPS1* | | Homozygous mutation c.1812_1813del (p.Glu604Aspfs*31) |
| | Citrullinemia | 1 | *ASS1* | Homozygous mutation c.370G>A (p.Asp124Asn) | |
| | HIBCH | 8 | *HIBCH* | | Homozygous mutation c.860A>G, (p.Asp287GIy) |
| | mitochondrial short chain enoyl - CoA hydratase 1 deficiency | 2 | *ECHS1* | | combound heterozygous c.410_411del (p. Tyr137Cysfs*7) AND c.268G>C (p.Gly90Arg) |
| | glutaric aciduria type 1 | 1 | *GCDH* | Homozygous mutation c.877G>A (p.A293T) | |
| | D-2- hydroxyglutaric aciduria 2 | 2 | *IDH2* | | Heterozygous mutation c.968G>A (p.Gly323Asp) |
| | glutaric aciduria type 2 | 1 | *ETFDH* | Homozygous mutation c.1130T>C (p.Leu377Pro) | |
| fatty acid oxidation | VLCAD | 1 | *ACADVL* | Homozygous mutation c.553G>A (p.Gly185Ser) | |
| | VLCAD | 3 | *ACADVL* | | Homozygous mutation c.507_527del, (p.Met169_Gly175del) |
| | CPT1 | 2 | *CPT1 A* | Homozygous mutation c.1393G>T (p.Gly465Trp) | |
| | CPT2 | 2 | *CPT 2* | | Homozygous mutation c.161T>G (p.Ile54Ser) |
| | primary systemic carnitine deficiency | 1 | *SLC22A5* | Homozygous mutation c.760C>T (p.Arg254*) | |
| others | pyridoxine-dependent epilepsy | 1 | *ALDH7A1* | Homozygous mutation c.328C>T (p.Arg110) | |
| LSD | MPS II | 1 | *IDS* | Hemizygous mutation c.1122C>T p.(=) | |
| | MPS II | 1 | *IDS* | Hemizygous mutation c.1327C>T (p.Arg443) | |
| | MPS III b | 2 | *NAGLU* | | Homozygous mutation c.14C>T (p.A5V) |
| | MPS III C | 2 | *HGSNAT* | Homozygous mutation c.1516C>T (p.Arg506*) | |
| | MPS IV a | 2 | *GALNS* | Heterozygous mutation c.697G>A (P.D233N) | Heterozygous mutation c.633+36G>A |
| | MPS VI | 1 | *ARSB* | Homozygous mutation c.923G>A (p.Gly308Glu) | |

| | | | | | |
|---|---|---|---|---|---|
| | GM1 gangliosidosis | 1 | *GLB1* | Homozygous mutation c.716C>T (p.Thr239Met) | |
| | Galactosialidosis | 7 | *CTSA* | | Homozygous mutation c.607C>A, (p.Pro203Thr) |
| | Tay Sachs disease | 2 | *HEXA* | Heterozygous mutation c.2T>C (p.Met1Thr) and Heterozygous mutation +c.7 8G>A (P.Trp26) | |
| | Fucosidosis | 2 | *FUCA1* | Homozygous mutation c.203C>T (p.Ser68Leu) | |
| | Nieman pick type A/B | 3 | *SMPD1* | Homozygous mutation c.1493G>A; (p.Arg498His) | |
| | Nieman pick type c | 1 | *NPC1* | Homozygous mutation c.3100G>A (p.Gly1034Arg) | |
| | Mucolipidosis type II | 1 | *GNPTAB* | Homozygous mutation c.3503_3503delTC | |
| | Mucolipidosis type II | 2 | *GNPTAB* | | Homozygous mutation c.2915+4_2915+9 delAGTCTT |
| | Fabry | 1 | *GLA* | | Hemizygous mutation c.937G>A (p.Asp313Asn) |
| glycogen storage disease | GSD Ia | 1 | *G6PC* | Homozygous mutation c.508C>t (p.Arg170*) | |
| | GSD Ib | 3 | *SLC37A4/ G6PT1* | | Homozygous mutation c.1042_1043delCT (p.Leu348Valfs*53) |
| | GSD II | 1 | *GAA* | Homozygous mutation c. 2560C>T (p.Arg854*) | |
| | GSD II | 4 | *GAA* | Homozygous mutation c.1327-2A>G | |
| | GSD II | 2 | *GAA* | Homozygous mutation c. 1802C>T (p.Ser601Leu) | |
| | GSD III | 4 | *AGL* | | Homozygous mutation c.772T>C (p.Ser258Pro) |
| Mitochondrial diseases | beta ketothiolase deficiency | 1 | *ACAT1* | | Homozygous mutation c.[412_419del CAAAGTCT];[412_419delCAAAGT CT], P.[Q138yFS*36];[Q138Yfs*36 |
| | PDH deficiency | 1 | *PDHA1* | | Heterozygote mutation E188K(G562A) |
| | pyruvate carboxylase deficiency | 1 | *PC* | Homozygous mutation c.2473+2_2473+5del | |
| | Mitochondrial DNA depletion syndrome type 3 | 2 | *DGUOK* | | Homozygous mutation c.152A>G (p.Lys51Arg) |
| | Mitochondrial DNA depletion syndrome type 3 | 1 | *DGUOK* | | Homozygous mutation G30325A |
| | Mitochondrial DNA depletion syndrome type 3 | 2 | *DGUOK* | Homozygous mutation c.352C>T (p.Arg118Cys) | |
| | Leigh disease | 1 | *SURF1* | | Homozygous mutation c.[805_833+2delinsGTTAG] [805_833+2delinsGTTAG] |
| | Leigh disease | 1 | *NDUFS4* | Homozygous mutation c.350+1G>A | |
| | Complex I | 2 | *NDUFV1* | Homozygous mutation c.1268C> T, T.T423M | |
| | Mitochondrial depletion syndrome, encephalomyopathic form with methylmalonic aciduria | 2 | *SUCLA2* | | Homozygous mutation c.502T>G (p.Tyr168Asp) |
| | Complex II | 4 | *SDHAF1* | | Homozygous mutation c.184c>T(p. Gln62) |
| | RRM2B-related mitochondrial disease | 1 | *RRM2B* | | Homozygous mutation c.424G>A (p.Asp142Asn) |
| | Mitochondrial DNA depletion syndrome type 6 | 2 | *MPV17* | | Homozygous mutation c.278A>C (p.Gln93Pro) |
| | nuclear mitochondrial complex III deficiency type 6 | 2 | *CYC1* | | Homozygous mutation c.496_516del (p.Met166_Phe172del) |
| | combined oxidative phosphorylation deficiency 10 | 4 | *MTO1* | | Homozygous mutation c.1762C>G (p.Leu588Val) |
| Perixosomal | peroxisomal acyl-CoA oxidase deficiency | 1 | *ACOX1* | | Homozygous mutation c.1469G>A (p.Arg490His) |
| NCL | NCL type 8 | 1 | *MFSD8* | | Homozygous mutation c.863+1G>A |
| **Total** | | **124** | | | |

On the other hand, our finding might be underestimated because a good number of cases could have been missed as our study population was based on clinical suspicion of referred cases to our center only. Furthermore, the absence of a neonatal screening program may have added to this assumption. Another factor that had contributed to this underestimation is non-Bahraini patients for whom limited tests could be carried out, as most of these tests are often expensive and not affordable.

The percentage of consanguinity was high among all patients, which is higher than that of the general population in Bahrain[11]. This high rate of consanguinity among our IEM patients might have played a significant role in increasing the frequency of occurrence of what are otherwise rare recessively inherited disorders. The consanguinity rate observed was similar to those reported in Omani and Jordanian study population groups, 90% and 95% respectively[12,13].

In our study, amino acids and organic acid disorders were the most prevalent disorders. Methylmalonic acidemia was the most common, unlike Saudi Arabia where propionic academia was reported to be the most common among organic acidopathies[10]. 3-hydroxyisobutyrl-CoA (HIBYL) hydroxylase is responsible for hydrolysis of HIBYL-CoA, a valine catabolite, as well as the hydrolysis of beta-hydroxy propionyl-CoA, an intermediate metabolite in the minor pathway of propionate metabolite; its deficiency is very rare worldwide[14].

However, in our study, HIBCH deficiency was the second most common disorder. We also reported another rare disease entity which is lysinuric protein intolerance, a disease that could be missed as familial hemophagocytic lymphohistiocytosis which was found in 4 patients of our sample[15].

The second most common group of IEMs disorders was LSD, this finding is dissimilar to the Kingdom of Saudi Arabia, where it has been reported as the most common disease entity in two separate studies[10,16]. Mucopolysaccharidosis type III (MPS III) constitutes the highest number of patients among this category followed by galactosialidosis, a disease which is considered rare worldwide[17].

Respiratory chain disorders were found in 18.6% of our total patients, prevalence of 2.9/100,000 in Bahrain. A significantly higher figure of 58.6/100,000 was found in Australian families of Lebanese origin[18]. We believe that this difference is probably attributed to the criteria used to include patients with suspicion of respiratory chain disorders (RCD). Our patients were diagnosed on the basis of either respiratory chain complexes enzyme assay on muscle biopsy and or molecular genetic evaluation, while the Australian patients were diagnosed using Bernier et al clinical criteria[19]. An accurate estimate of its prevalence in our country is still complicated. It is likely that many patients with RCD are not referred for investigation, as initial symptoms are often non-specific and can masquerade as other diseases. RCD are also claimed to occur with a frequency of 5.7/100,000 in Western Sweden and 4.7/100,000 in Finland[20].

Molecular genetic testing was performed for 65.9% of our patients. Compound heterozygous mutations were detected only in 9 (7.2%) of our patients, this low percentage is related to high consanguinity among our population where homozygous mutations are usually higher[21]. In our patients with methylmalonic acidemia, Metabolism of Cobalamin Associated B (MMAB) gene was the most common detected which has a proportion of 12% of isolated MMA genes internationally[22].

In HIBCH and galactosialidosis, we detected two shared novel mutations (c.860A>G, p.Asp287GIy and c.607C>A, p.Pro203Thr) respectively among patients of Bahraini origin belonging to different families. This could be attributed to founder mutations that are distinct to our population. WES was helpful in detecting complex neuro-metabolic diseases especially a disease related to RCD, where their clinical picture may mimic other diseases[23,24]. It is important to identify the spectrum of genetic mutations in all our patients.

In our study, we defined the outcome as a percentage of death, which was 41.5% among total diagnosed cases. The highest percentage of death in our patients was among respiratory chain disorders (65.7%). This finding could be explained by the nature of this disease category in relation to multi-organ involvement, late diagnosis, and limited specific treatment options. There was no data about the outcome from the neighboring countries for comparison. However, Debray et al reported a death rate of 46% among their patients diagnosed with RCD[24]. The second most common category of death was among glycogen storage diseases (57.9%). GSD type II had 100% death rate. Our patients diagnosed with this disease were of the severe infantile type, which is associated with the GAA gene mutation that is considered as cross-reactive immunological materials (CRIM) negative and usually has high a mortality rate[25].

The study is limited because of being retrospective; some cases could be missed due to poor documentation or improper classification codes. A registry of cases of IEM has been initiated during the course of this study, which would track more cases and their related families. Newborn screening would serve to provide early detection of IEM, and hence strengthen the accuracy of our data.

## CONCLUSION

**Our study revealed a high prevalence rate of IEM in Bahrain including rare disorders, such as HIBCH and galactosialidosis. The most common disorders in our study were diagnosed using TMS, which emphasizes the need in implementing a national neonatal screening program and national registry for metabolic disorders that aims in early disease detection and early management. Confirming the diagnosis of these disorders by molecular genetic testing helps to plan a prevention program through preimplantation genetic diagnosis.**

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