Molecular Genetics and Metabolism Reports 39 (2024) 101083

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Inherited metabolic disorders in Cyprus

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ARTICLE INFO

Keywords:
Inherited metabolic disorders
Inborn errors of metabolism
Selective screening
Registry
Prevalence
Cyprus

ABSTRACT

Selective screening for inherited metabolic disorders (IMD) began in Cyprus in 1990. Over the last thirty-three years 7388 patients were investigated for IMD and 200 diagnoses were made (diagnostic yield 2.7%). The existence of a single laboratory of Biochemical Genetics for the whole island facilitated the creation of a national registry for IMD. The minimal prevalence of IMD in Cyprus is 53.3 cases per 100,000 live births. The most common group are disorders of amino acid metabolism (41.0%), followed by disorders of carbohydrate metabolism (16.5%), disorders of complex molecule degradation (16.5%), mitochondrial disorders (10.5%) and disorders of vitamin and co-factor metabolism (5.5%). Hyperphenylalaninaemia is the most common IMD (14.0%) followed by galactosaemia (7.0%), glutaric aciduria type I (5.5%) and MSUD (4.0%). Some disorders were found to have a relatively high incidence in specific communities, for example Sandhoff disease among the Cypriot Maronites and GM1 gangliosidosis in one particular area of the island. Other disorders were found to have a relatively higher overall incidence, compared to other Caucasian populations, for example galactosaemia, glutaric aciduria type I and MSUD, while fatty acid oxidation defects, Gaucher disease and classic PKU were found to have a relatively lower incidence. Molecular characterization of selected disorders revealed many novel genetic variants, specific to the Cypriot population.

1. Introduction

Inherited metabolic disorders (IMD) are a diverse group of more than 1400 disorders [1] which, although individually rare, collectively are quite common affecting more than one in every 1000 newborns [2]. Prompt diagnosis is crucial for the treatment and management of these disorders. Several attempts at establishing a classification of IMD have been made over the years, with the most recent being the International Classification of Inherited Metabolic Disorders, ICIMD [1].

A small number of IMD are diagnosed through national newborn screening programmes, the number varying in different countries from 1 to more than 50 [3]. The majority of IMD, however, are diagnosed through selective screening among patients, both children and adults, who have clinical symptoms suggestive of an inherited metabolic disorder. From the beginning of the twentieth century when the first inherited metabolic disorders were described by Archibald Garrod, until relatively recently, selective screening was mainly based on biochemical investigation, through the measurement of metabolite concentrations and enzyme levels in body fluids and tissues. With the advent of the techniques of recombinant DNA technology in the mid 1980's, mutation analysis started supplementing the biochemical investigation and aiding in the diagnosis of IMD. The more recent techniques of Next Generation

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https://doi.org/10.1016/j.ymgmr.2024.101083
Received 9 February 2024; Received in revised form 15 April 2024; Accepted 16 April 2024

Sequencing (NGS) and Metabolomics have been added to the repertoire of diagnostic methods and have led to the identification of a great number of novel conditions [4]. Even with a primary genetic diagnosis, biochemical tests remain essential for confirming functional effects of novel genetic variants and for monitoring treatment.

Cyprus is a small country (9251 km^2) with a population of around 0.9 million, having one Reference Children's Hospital and one laboratory of Biochemical Genetics. This allows for a central national registry of all cases diagnosed, and for accurate epidemiological studies. It also facilitates the identification of characteristic features, such as increased frequency of specific disorders in the population or a sub-section of the population, and the optimization of laboratory and clinical services.

In this study we present the spectrum of inherited metabolic disorders diagnosed in Cyprus in the last thirty-three years.

2. Methods

Children with a suspicion for an IMD were referred to the Children's Reference Hospital, Archbishop Makarios III, in Nicosia. Adults suspected of an IMD were seen at the Cyprus Institute of Neurology and Genetics and other public and private hospitals and clinics.

Until the early 1990's laboratory investigation for IMD was not possible in Cyprus. The first step was the establishment of collaborations with laboratories abroad so that samples could be sent for metabolic tests. At the same time, the infrastructure for a local laboratory of biochemical genetics started being set up at the Cyprus Institute of Neurology & Genetics, and Cypriot scientists were appropriately trained abroad. In less than ten years the core diagnostic tests were available locally, while collaborations with laboratories abroad for the remaining tests continued. The Biochemical Genetics laboratory participates in ERNDIM and CAP External Quality Control Schemes and has been accredited to ISO15189 since 2014.

The population studied is the population residing in the Government controlled area which includes Greek Cypriots (77.8% of the population), the three minority groups, Maronites, Armenians and Latins (1.1%) as well as people of other ethnicities living in Cyprus for various reasons (21.1%).

The study includes cases diagnosed through selective screening by the reference laboratory as well as cases of hyperphenylalaninaemia detected through the National Newborn Screening Programme and confirmed by the reference laboratory. Newborn screening for PKU and congenital hypothyroidism is carried out by The Centre for Preventive Paediatrics "Americos Argyriou" since 1990. No other IMD is included in the National Newborn Screening Programme.

The great majority of diagnoses were confirmed by enzyme measurement or DNA analysis or both, while the remaining cases had a pathognomonic metabolite profile.

3. Results and discussion

Over the last thirty-three years a total of 7388 patients were investigated for IMD, 86%. were infants or children and 14% adults. 96.5% of the patients were Cypriots and 3.5% were non-Cypriots. A total of 200 diagnoses were made, corresponding to a diagnostic yield of 2.7%. The age of the patients at diagnosis ranged from 4 days to 69 years. Sixty-six different disorders were diagnosed (Table 1). Of the diagnosed cases 161 were Greek Cypriots (80.5%), 34 were foreigners (17.0%) and 5 had one Cypriot and one foreign parent (2.5%). There was a male predominance among the diagnosed patients with a male to female ratio of 1.2 (m:f ratio in the cohort studied 1.6). Of the 200 cases, 160 are alive today and 40 have died (20.0%).

The minimal prevalence of IMD in Cyprus is 53.3 per 100,000 live births (95% Confidence Interval 45.1–61.3). This value was obtained from the number of patients with IMD born in Cyprus between 1990 and

Table 1
Inherited metabolic disorders diagnosed in Cyprus 1990–2022.

Category according to ICIMD/Disorder	Number of cases	Comments
Disorders of amino acids metabolism	**82**	
Hyperphenylalaninaemia	28	4 classic, 3 mild PKU, 21 mild HPA
Maple Syrup Urine Disease	8	3 novel variants [11]
Non-ketotic hyperglycinaemia	6	
Cystinuria	5	28 patients were diagnosed by another group [30]
Ornithine transcarbamylase deficiency (OTC)	5	One family
Carbamylphosphate synthase deficiency (CPS I)	2	
Argininosuccinic aciduria	1	
Alkaptonuria	2	
Cystinosis	1	
Albinism	1	
Hyperprolinaemia I	1	
Homocystinuria	1	
Glutaric aciduria type 1	11	2 novel variants [13]
Methylmalonic aciduria	4	Mutase deficiency
Ethylmalonic encephalopathy	3	New biochemical marker identified [31]
Propionic aciduria	1	
Aminoacylase 1 deficiency	1	
Short/branched chain AcylCoA DH deficiency	1	
Disorders of complex molecule degradation	**33**	
GM1 gangliosidosis	4	
Tay-Sachs disease	3	One juvenile case [32]
Gaucher disease (type I)	3	A novel intronic variant identified [28]
Saposin B deficiency	3	
Mucolipidosis type III	3	
Sandhoff disease	2	3 more patients diagnosed before 1990. Two novel variants [14,15]
Farber disease	2	
Niemann Pick A/B	2	
Neuronal ceroid lipofuscinosis	2	
Aspartylglucosaminuria	2	
Fabry disease	1	Female with minimal symptoms [33]
Hurler (MPS I)	1	
Hunter (MPS II)	1	
Sanfilippo (MPS III B)	1	

(*continued on next page*)

Table 1 (*continued*)

Category according to ICIMD/Disorder	Number of cases	Comments
Maroteaux-Lamy (MPS VI)	3	
Disorders of carbohydrate metabolism	**33**	
Galactosaemia	14	Novel deletion accounts for 55% of disease alleles [17,18]
Fructose 1,6-biphosphatase deficiency	3	
Aldolase B deficiency	2	
Glycogen storage disorder type 0	1	
Glycogen storage disorder type I	1	
Glycogen storage disorder type II (Pompe)	6	4 belong to the same family and are asymptomatic [34]
Glycogen storage disorder type V	4	Novel variant identified [35]
Glycogen storage disorder type IXa	2	
Mitochondrial disorders	**21**	
mtDNA depletion syndrome	8	POLG
Complex I deficiency	1	
Complex IV deficiency	4	
Complex V deficiency	1	
Pearson's syndrome	1	
MELAS	1	
YME1L1 deficiency	2	Second family worldwide [36]
TRNT1 deficiency	1	
Creatine transporter deficiency	2	
Disorders of vitamin and co-factor metabolism	**11**	
Cobalamin C defect	5	
Segawa disease	3	
Biotinidase deficiency	2	
Molybdenum Co-factor deficiency	1	
Disorders of lipid metabolism	**10**	
Adrenomyeloneuropathy	4	
Lipin-1 deficiency	2	
Zellweger spectrum disorder	1	
Cerebrotendinous xanthomatosis	1	
Sjögrenn-Larsson syndrome	1	
Chanarin-Dorfan syndrome	1	
Disorders of nucleobase, nucleotide and nucleic acid metabolism	**3**	
Dihydropyrimidine dehydrogenase deficiency	3	
Disorders of trace elements and metals	**2**	
Defect of the CTR1 copper transporter	2	New disorder [22]
Neurotransmitter disorders	**2**	
Succinic semialdehyde DH deficiency	2	
Disorders of fatty acid and ketone body metabolism	**1**	
Mitochondrial trifunctional protein deficiency	1	
Disorders of peptide and amine metabolism	**1**	
Glutathione synthase 1 deficiency	1	
Disorders of lipoprotein metabolism	**1**	
Tangier disease	1	

2022 and the total number of live births for the same period (309,826, Statistical Services, Government of Cyprus). We call it the minimal prevalence because some cases may have been missed, either because they did not present with clinical symptoms or because they were not referred for laboratory investigation. Furthermore, we know that a number of cases of cystinuria, dyslipidaemias and haemochromatosis have been diagnosed by other laboratories. The global birth prevalence of all IMD was estimated as 50.9 per 100,000 live births, based on results of 27 studies from 21 countries with values ranging from 6.75 in Germany to 311.27 in Singapore [5].

The number of diagnoses per year is shown in Fig. 1. We have adopted the ICIMD [1] to assign the disorders identified to specific categories. The most common group are disorders of amino acid metabolism (41.0%), followed by disorders of carbohydrate metabolism (16.5%), disorders of complex molecule degradation (16.5%), mitochondrial disorders (10.5%) and disorders of vitamin and co-factor metabolism (5.5%) (Fig. 2). Hyperphenylalaninaemia was the most frequently diagnosed IMD (14.0% of total diagnoses) followed by galactosaemia (7.0%), glutaric aciduria type I (5.5%) and MSUD (4.0%) (Fig. 2).

Disorders of amino acid metabolism (category 1 according to the ICIMD, http://www.icimd.org) was the most common group of IMD diagnosed in Cyprus, 41% of total diagnoses, similar to other European countries [6,7]. The most frequently diagnosed IMD in Cyprus was hyperphenylalaninaemia, accounting for 14.0% of all cases, again similar to other European countries; Austria 17.7% [6], Estonia 21.6% [7]. In the period 1989–2010, 182,837 newborns were screened through the national newborn screening programme and 14 cases of hyperphenylalaninaemia (HPA) were detected, giving an incidence of 1:13,000 live births [8]. No case of classic PKU was detected up to that time, only mild PKU (35.7%) and mild HPA (64.3%). Between 2011 and 2022, 14 more cases were detected of which 10 were HPA and 4 were classic PKU. Molecular analysis detected the presence of 21 previously described variants, all in compound heterozygosity, the most common being the p.Ala395Gly variant, accounting for 13% of the alleles. Of the four classic cases only one is Cypriot, the other three are children of other nationalities. Thus, although the incidence of hyperphenylalaninaemia (all types) is similar to that of many European countries [9] classic PKU seems to be rare among Cypriots. This finding is in agreement with the gradient in genotype and phenotype distribution that exists across Europe, from classic PKU in the northeast to mild PKU in the southwest and mild hyperphenylalaninaemia in the south [9].

The second most common disorder within the category of aminoacidopathies is maple syrup urine disease (MSUD), with a live birth incidence of about 1:40,000. This incidence is higher than the worldwide incidence of 1 in 185,000 based on data from neonatal screening [10]. Eight patients were diagnosed, seven with the classic form and one

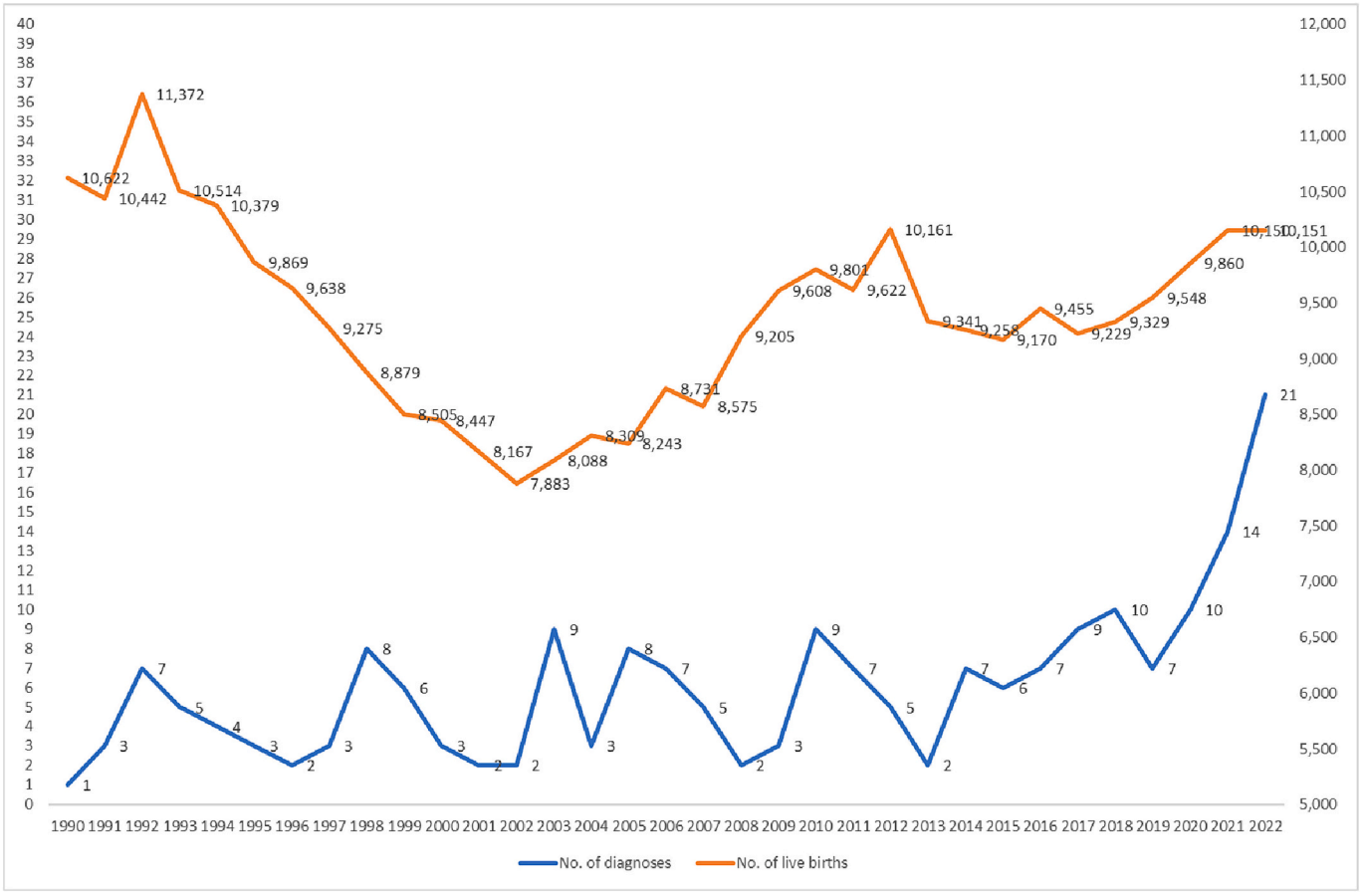

Fig. 1. The number of diagnoses (left axis, blue line) and the number of live births (right axis, yellow line) per year.

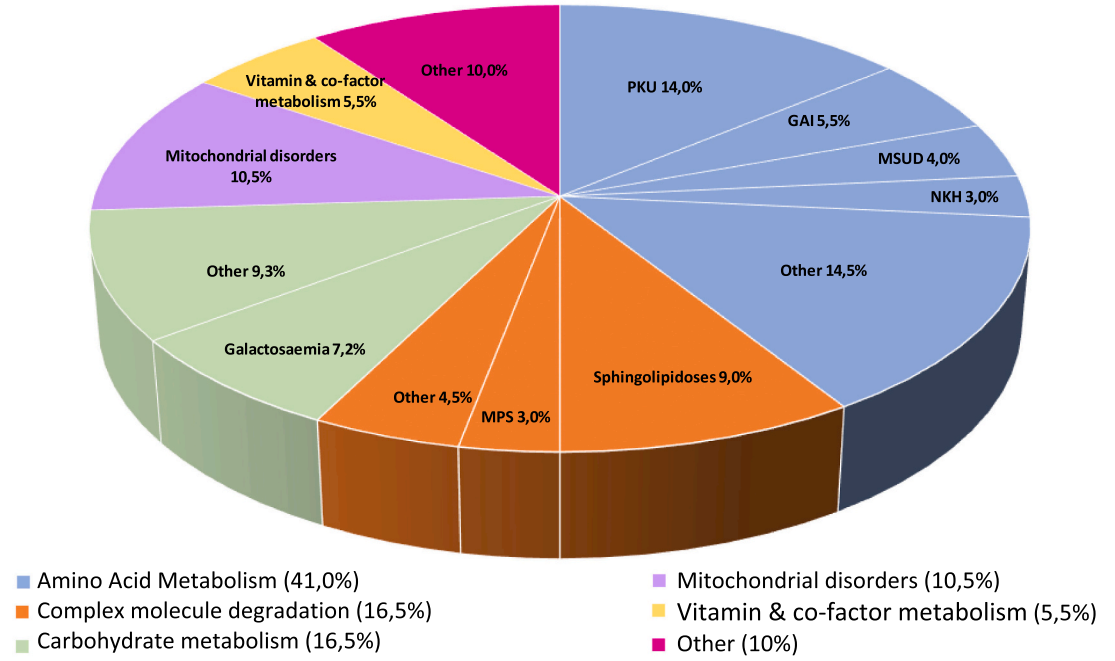

Fig. 2. Inherited metabolic disorders diagnosed in Cyprus (% of total diagnoses).

with the intermittent form. A molecular study of the first five Greek-Cypriot patients diagnosed revealed five different pathogenic variants, three of which were novel [11]. Three of the variants are in the *BCKDHA* gene and two in the *BCKDHB* gene. The intermittent form was detected through newborn screening by a private laboratory and was found to carry the variants p.Gly278Ser and p.Asn176Lys in the *BCKDHB* gene.

Most of the organic acidurias are included in the category of disorders of amino acid metabolism in the ICIMD. The most common organic aciduria detected in Cyprus was glutaric aciduria type I, with an incidence of about 1 in 30,000 which is higher than the incidence reported from newborn screening programmes across the world (between 1 in 65,000 and 1 in 181,000 [12]. Five missense variants were identified, of which two were novel and account for 76.5% of disease alleles [13]. Other organic acidurias detected were methylmalonic aciduria (4 cases of mutase deficiency), ethylmalonic encephalopathy (3 cases), propionic aciduria (1 case), aminoacylase 1 deficiency (1 case) and short/branched chain AcylCoA dehydrogenase deficiency (1 case).

The urea cycle disorders are also included in the category of disorders of amino acid metabolism. We diagnosed five cases of ornithine transcarbamylase deficiency, two cases of carbamylphosphate synthase I (CPSI) deficiency and one case of arginosuccinic aciduria. Other disorders within this category that were diagnosed were: non-ketotic hyperglycinaemia (6 cases), cystinuria (5 cases), alkaptonuria (2 cases), cystinosis (1 case), albinism (1 case), hyperprolinaemia (1 case) and homocystinuria (1 case).

The second most common disorder categories are those of carbohydrate metabolism and complex molecule degradation, representing 16.5% of total diagnoses each (Table 1 and Fig. 2). Sandhoff disease and GM1 gangliosidosis were found to be relatively common in two communities. The incidence of Sandhoff disease was found to be particularly high among Cypriot Maronites, 1 in 7 being a carrier of a founder mutation [14]. The Maronite community is a small community (about 0.5% of the population) that migrated to Cyprus from Syria and Lebanon between the 8th and 13th centuries and lived isolated for many years, maintaining a high degree of consanguinity. Two Maronite patients with Sandhoff disease were diagnosed within the study period and two more cases were diagnosed before 1990. Only one case of Sandhoff disease was diagnosed among the Greek Cypriots, before the study period, and this was found to carry a novel pathogenic variant [15].

GM1 gangliosidosis was found to have a high incidence in one particular area on the Troodos mountains, with a carrier frequency of 1 in 12 [16]. A single pathogenic variant (p.Arg482His) was found to be responsible for all disease alleles, and this can be attributed to geographical isolation in the past and consanguinity. It is interesting that the variant responsible for GM1 gangliosidosis in Cyprus is the same as the variant responsible for GM1 gangliosidosis in Malta, something which might be related to the historic connections between the two islands. Four patients with GM1 gangliosidosis were diagnosed within the study period. Other diagnoses belonging to this disorder category include Tay-Sachs disease (3 cases), Gaucher disease type I (3 cases), saposin B deficiency (3 cases), mucolipidosis type III (3 cases), Niemann Pick A/B (2 cases), Farber disease (2 cases), neuronal ceroid lipofuscinosis (2 cases), aspartylglucosaminuria (2 cases), Fabry disease (1 case), MPSI (1 case), MPS II (1 case), MPSIIIB (1 case) and MPS VI (3 cases).

Disorders of carbohydrate metabolism accounting for 16.5% of diagnoses (Table 1 and Fig. 2). The most common disorder in this group is classic galactosaemia, with an incidence of about 1:31,000 [17]. A novel variant, a deletion of 8.5 kb in the *GALT* gene, was identified. This deletion is very interesting because, in addition to abolishing the whole of the *GALT* gene, it also extends into the adjacent interleukin 11 receptor alpha gene (*1L11RA*) resulting in additional phenotypic abnormalities such as craniosynostosis and microcephaly [18]. The deletion is responsible for 55% of disease alleles. Four other variants were detected, with the p.Lys285Asn accounting for 30% of disease alleles. It is interesting that the p.Gln188Arg variant, which is the most common variant in Caucasian populations, was not detected among Greek Cypriots [17], but we did find it recently in a patient with a Romanian mother. One Russian patient was diagnosed with Duarte galactosaemia through newborn screening by a private laboratory. Other disorders within this category were fructose 1,6-biphosphatase deficiency (3 cases), aldolase B deficiency (2 cases) and 14 cases of glycogen storage disorders (Table 1).

Eighteen patients were diagnosed with mitochondrial disorders, eight of whom had mtDNA depletion syndrome with pathogenic variants in the *POLG* gene (Table 1). This number is an under-estimate as we know that a number of patients, mostly adults, was diagnosed with a mitochondrial disease by another group (results not published).

Eleven patients were diagnosed with a disorder of vitamin or cofactor metabolism (Table 1). Five patients had a cobalamin C defect, giving an incidence of about 1 in 62,000 which is higher than the estimate of 1:100,000 to 1:200,000 for North America [19].

Ten patients were diagnosed with a disorder of lipid metabolism, five with a peroxisomal disorder, two with Lipin-1 deficiency, one with cerebrotendinous xanthomatosis, one with Sjögrenn-Larsson syndrome and one with Chanarin-Dorfman syndrome. Three patients were diagnosed with a pyrimidine disorder.

Regarding disorders of fatty acid and ketone metabolism, one case of mitochondrial trifunctional protein deficiency was diagnosed. No case of medium chain acyl-CoA dehydrogenase deficiency (MCADD) was detected, despite the fact that many patients with relevant symptoms were investigated by acylcarnitine and organic acid analysis in our laboratory. MCADD is one of the most common IMD in Caucasian populations with an average incidence of about 1 in 10,000 [20]. One could speculate that patients with mild variants do exist but did not present clinically during the study period.

No patient with a glycosylation defect was identified, despite the fact that many patients were investigated and samples were sent abroad for transferrin isoelectric focusing. Glycosylation defects are rare in Europe with an estimated prevalence of 0.1–0.5 cases per 100,000 persons [21].

A novel disorder involving a defect in the CTR1 copper transporter was identified in a pair of Greek Cypriot twins. This disorder was fully characterized at the clinical, biochemical and molecular level [22].

The population of Cyprus (Government controlled area) increased from 0.58 million in 1990 to 0.92 million in 2021 (Statistical Services, Government of Cyprus). During this period the proportion of non-Cypriots living in Cyprus increased significantly, mainly due to migration from Russia, Eastern European countries and Middle-Eastern countries, particularly Syria. The proportion of foreigners living in Cyprus in 2021 was 21.1% of the population (Statistical Services, Government of Cyprus). The annual number of births decreased from 10,622 in 1990 to 7,883 in 2002, then increased to 10,161 by 2012 and thereafter stabilized at about this level (Fig. 1). The number of diagnoses was 42 in the first ten years of the study and 90 in the last ten years. The increase in the number of diagnoses can be attributed to several factors. There was an increase in awareness for inherited metabolic disorders among paediatricians and other doctors, which resulted in an increase of referrals for laboratory investigation. Also, the increase in the number of diagnostic tests available locally lead to a more liberal use, compared to ordering tests that had to be sent abroad. A significant contribution also comes from the increase in the number of non-Cypriots living in Cyprus, particularly people from the Middle East, who have a high rate of consanguinity and large families. Of the 90 cases diagnosed in the last ten years 25 (28%) were non-Cypriots and 5 were patients with one Cypriot parent and one foreign parent (5.5%). The wider use of NGS, particularly in the last two years, has also contributed to the increase in the number of diagnoses, with many patients being diagnosed through NGS first and then confirmed biochemically.

The Cypriot population has a unique genetic composition which differs significantly from that of its neighbours [23]. This was the result of enrichment of the local genetic pool by the genes of numerous "visitors" to the island, whether as conquerors (Persians, Arabs, Franks, Venetians and Turks) or as immigrants (Maronites, Armenians). Founder effects have been described for many genetic disorders in addition to Sandhoff's and GM1 gangliosidosis: familial Mediterranean fever [24], cystic fibrosis [25], Friedreich's ataxia [26] and 21-hydroxylase deficiency [27].

Our study has shown that some inherited metabolic disorders occur

with an increased frequency, either in the whole population, for example galactosaemia and glutaric aciduria type I, or in specific clusters, such as Sandhoff disease and GM1 gangliosidosis. Other conditions occur with a lower frequency than in most Caucasian populations. Classic PKU is rare among Greek Cypriots [8] and so is Gaucher disease [28,29]. Some IMD have not been detected at all during the study period, for example MCADD and disorders of glycosylation. The same phenomena that can explain the presence of severe variants and the high frequency of certain disorders, can also account for the presence of mild variants and the low frequency of other disorders. These phenomena include the founder effect and genetic drift, as well as geographic isolation.

The present study has described the spectrum of IMD present in Cyprus and has provided useful information for health policy planning. The number of patients diagnosed with an IMD in Cyprus is expected to rise in the coming years, with the imminent introduction of expanded newborn screening and the wider use of NGS.

Ethics statement

All procedures followed were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained for genetic studies (DNA analysis).

Funding information

This work was mainly funded by the Cyprus Institute of Neurology and Genetics. Specific projects were funded by Telethon Cyprus and by the Cyprus Research Promotion Foundation (Project PENEK/0609/64 was co-financed by the European Regional Development Fund and the Republic of Cyprus).

Credit authorship contribution statement

Theodoros Georgiou: Writing – review & editing, Methodology, Investigation. **Petros P. Petrou:** Writing - review & editing, Methodology, Investigation. **Anna Malekkou:** Methodology, Investigation. **Ioannis Ioannou:** Investigation. **Marina Gavatha:** Investigation. **Nicos Skordis:** Investigation. **Paola Nicolaidou:** Investigation. **Irini Savvidou:** Investigation. **Emilia Athanasiou:** Investigation. **Sofia Ourani:** Investigation. **Elena Papamichael:** Investigation. **Marios Vogazianos:** Investigation. **Maria Dionysiou:** Investigation. **Gabriella Mavrikiou:** Investigation. **Olga Grafakou:** Investigation. **George A. Tanteles:** Investigation. **Violetta Anastasiadou:** Investigation, Conceptualization. **Anthi Drousiotou:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

None.

Data availability

Data could be shared upon written request to the corresponding author.

Acknowledgements

This article is dedicated to the memory of Dr. Goula Stylianidou, paediatric neurologist at Archbishop Makarios III Hospital, Nicosia, who contributed significantly to this study from 1990 up to her untimely death in 2008.

We would like to acknowledge support of the study by other departments of the Cyprus Institute of Neurology and Genetics, namely the Department of Cytogenetics and Genomics, the Department of Neurogenetics, the Department of Molecular Genetics-Thalassaemia and the Department of Cancer Genetics, Therapeutics and Ultrastructural Pathology.

We would like to thank Ms. Kristiana Anninou for establishing and maintaining the Department's Database and Registry. We would also like to thank Ms. Christina Hadjiyianni for her excellent services as scientific secretary over the whole period of the study.

We would also like to express our deep gratitude to Professor Lefkos Middleton, currently at Imperial College, London, for establishing the Cyprus Institute of Neurology and Genetics in 1990, as the first biomedical research institute on the island, which made possible this and numerous other studies on genetic disorders in the Cypriot population.

Finally, we would like to thank all patients and their families.

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