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Gene Frequencies of Methylmalonic Acidemia Disease at the Global Level and Compiling the Pathogenic Mutations in the Iranian Population

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ABSTRACT

Background: Methylmalonic acidemia (MMA) is a rare autosomal recessive metabolic disorder resulting from a genetic defect in methylmalonyl-CoA mutase (MCM) or a defect in the biosynthesis of its cofactor, adenosyl-cobalamin (AdoCbl). The disease is caused by a mutation in six main genes (*MUT*, *MMAA*, *MMAB*, *MMADHC*, *MMACHC*, and *MCEE*). In this investigation, we estimate MMA-disease gene frequencies globally and report MMA-causative mutations in the Iranian population.

Materials and Methods: Human gene mutation database (HGMD) has been utilized to estimate MMA-disease gene frequencies. To compile MMA mutations in Iran, we systematically reviewed PubMed, Google Scholar, CIVILICA, Magiran, and SID databases to explore relevant articles in English and Persian.

Results: The frequencies of causative genes among MMA patients at the global level were as follows: *MUT* (64.14%), *MMACHC* (17.74%), *MMAA* (13.48%), *MMAB* (7.1%), *MMADHC* (2.9%), and *MCEE* (0.85%). Until February 11, 2024, 24 MMA mutations had been compiled from the Iranian population; of which 11 mutations (45.8%) had been diagnosed only in Iran and had not been addressed in other populations yet.

Conclusion: Collection and recognition of MMA mutations in the Iranian population can be helpful for early diagnosis and treatment before the onset of neurological manifestations in neonates.

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Introduction

Methylmalonic acidemia (MMA; OMIM#251000) is an autosomal recessive inherited inborn error of metabolism [1]. MMA is frequently produced by a lack of the enzyme methylmalonyl-CoA mutase (MCM; EC 5.4.99.2) or impairment in the biosynthesis of its cofactor, adenosylcobalamin (AdoCbl) [2]. Methylmalonyl-CoA mutase is an adenosylcobalamin (vitamin B12) dependent mitochondrial enzyme that catalyzes the isomerization of methylmalonyl-CoA into succinyl-CoA during the oxidation of propionate towards the Krebs cycle (Figure 1) [3, 4]. Therefore, abnormal accumulation of methylmalonate in body fluids is due to a deficiency in enzyme or apoenzyme biosynthesis [5].

Oberholzer et al. first characterized MMA at the Queen Elizabeth Hospital for Children [6]. Then, Stokke et al. reported several children who accumulated large amounts of methylmalonic acid in their blood, urine, and cerebrospinal fluid [7]. Isolated MMA is caused by a mutation in five genes: *MUT*, *MMAA*, *MMAB*, *MCEE*, and *MMADHC* [8, 9]. The first three genes account for more than 97% of MMA cases [10]. Another major gene, *MMACHC* (responsible for the joined MMA and hyperhomocysteinemia), is the frequent genetic disorder of cobalamin metabolism [11].

The reported incidence of MMA is estimated to be 1:48000 to 1:61000 newborns in the western population [12]. In countries with higher rates of consanguineous marriage, the incidence of the disease is expected to be higher. In Saudi Arabia, for example, the prevalence of MMA has been reported from 1: 2000 to 1: 5000 [13]. Table 1 presents the MMA incidences in the different countries. In most studies conducted on metabolic diseases, methylmalonic acidemia is the most common disease. Since limited studies have been undertaken on Iranian patients, the exact prevalence of this disease in Iran is not available [14, 15]. However, newborn screening programs in several countries provide relatively good estimates of the birth prevalence of MMA. For example, in some countries in the Middle East and North Africa region, due to the introduction of newborn screening programs for inherited metabolic disorders, the prevalence of diseases in this group, including methylmalonic acidemia, has decreased [16]. In this systematic review, we briefly describe genes causing MMA, the incidence of MMA worldwide, and its treatment. Then, we try to answer the following questions systematically: 1) What is the gene distribution of MMA mutations worldwide? and 2) What are the identified MMA-causing mutations in the Iranian population?

Metabolism of branched-chain amino acids

MCM plays a catalytic role in the isomerization of L-methylmalonyl-CoA into succinyl-CoA (Figure 2) [24, 25]. In MMA disease, as a congenital metabolic defect, a disorder occurs in propionate (propionyl CoA) oxidation in the Krebs cycle [4, 26]. This metabolic pathway is vital in the catabolism of BCAAs (branched-chain amino acids) such as methionine, threonine, isoleucine, valine, and odd-chain fatty acids or cholesterol [27]. MMA can result from two different classes of genetic defects. Those termed cbl have a defect in the genes needed for metabolizing the effective form of AdoCbl. The cbl form is a vitamin B12-responsive MMA [28]. The other form, mut, is involved in the gene encoding of the MCM apoenzyme [29, 30]. In other words, mut groups are vitamin B12-unresponsive MMA [25]. Biochemical studies

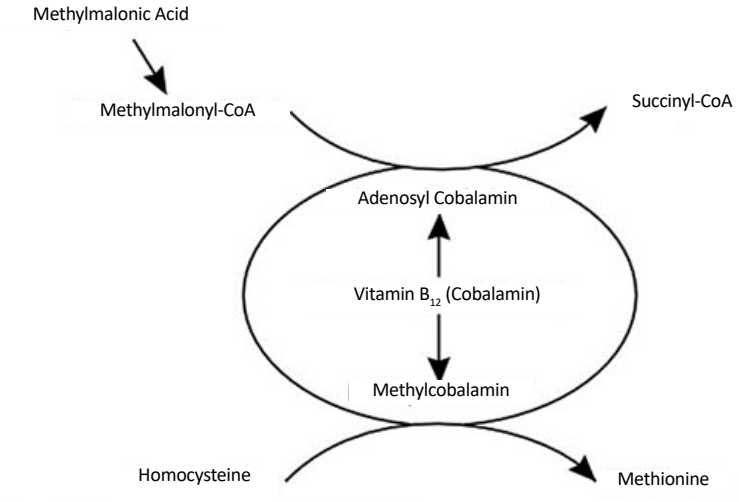

Figure 1. Cobalamin (vitamin B12), a cofactor in converting homocysteine to methionine and also methylmalonyl coenzyme A (CoA) to succinyl CoA [80]

Table 1. Prevalence of methylmalonic acidemia in different populations

Population	Incidence	Ref.
Worldwide	1:50000-1:100000	Ramsay et al. 2018 [17]
Western societies (West European, Australia, USA, Canada)	1:48000-1:61000	Baumgartner et al. 2014 [12]
Saudi Arabia	1:5000-1:2000	Ozand et al. 1994 [13]
Italy	1:115000	Melo et al. 2011 [18]
New Zealand	0.28:10000	Wilson et al. 2004 [19]
South Korea	0.1:10000	Park et al. 2016 [20]
United States of America	≈0.14:10000	Chapman et al. 2018 [21]
Germany	1:169000	Melo et al. 2011 [18]
Kuwait	≈0.16:10000	Chapman et al. 2018 [21]
Taiwan	1:850000	Cheng et al. 2010 [22]
Japan	1:50000	Shigematsu et al. 2002 [23]

on fibroblasts in patients with MMA have shown two subtypes due to deficiency or absence of MCM [3]: mut^0, which has no MCM activity, and mut- which indicates the abnormal and residual enzymatic activity of MCM [31].

The mature MCM enzyme is a homodimer protein with the N-terminal CoA binding and C-terminal cobalamin-binding domains [32, 33]. Other multiple functional domains also comprised a mitochondrial signal, a dimerization domain, and a linker region. *MMAA* and *MMAB* make a protein product as a cofactor (AdoCbl) for MCM activity [10].

Molecular genetics of methylmalonic acidemia

MMA is a heterogeneous genetic disorder. Table 2 presents the MMA-causing genes. In 60%-70% of affected patients with MMA, *MUT* mutations lead to MMA [31].

MUT

The *MUT* gene encodes the human MCM which is located on 6p12.3 with 13 exons expanding more than 35 kb [31, 32]. This gene encodes a protein with 750 amino acids (77.5

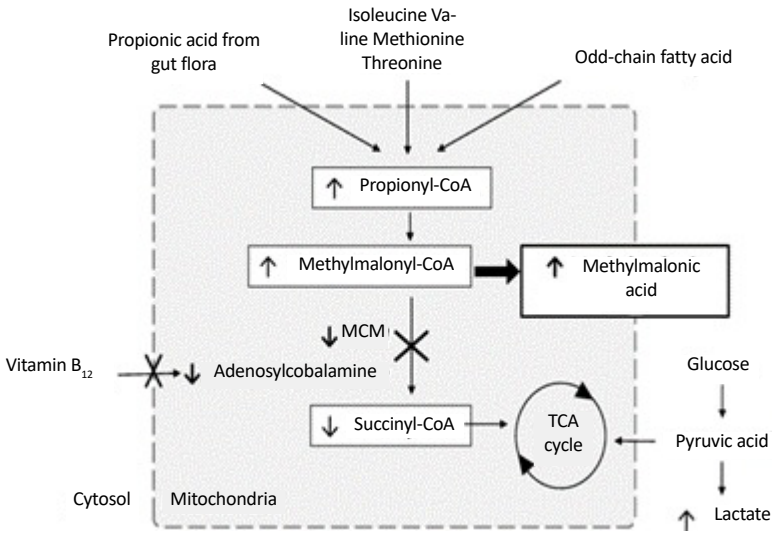

Figure 2. Metabolic pathway of methylmalonic acidemia

Note: MMA accrues systemically due to defects in the structure of intracellular methylmalonyl-CoA mutase (MCM) [81].

Table 2. List of the genes involved in methylmalonic acidemia

Gene	Cytogenetic Location	Transcript Number	Polypeptide	Exon	References
MUT	6p12.3	NM_000255.4	750aa	13	[31, 32]
MMAA	4q31.21	NM_172250.3	418aa	7	[37]
MMAB	12q24.11	NM_052845.4	250aa	9	[40]
MCEE	2p13.3	NM_032601.4	176aa	3	[41]
MMADHC	2q23.2	NM_015702.3	296aa	8	[43]
MMACHC	1p34.1	NM_015506.3	282aa	4	[45]

kDa) in the mitochondrial matrix [34]. The human *MUT* gene was first addressed by Ledley et al. [35]. It is important to note that at least 200 *MUT* mutations have been identified worldwide [36].

MMAA

MMAA is the common gene after *MUT* as the causative gene for MMA. The cblA type is caused by a mutation in the *MMAA* gene mapped to chromosome 4q31.21 with 7 exons and encoding 418 amino acids [37]. Two different functions are known for this gene. The first is the reduction of cobalamin II to cobalamin I by transporting vitamin B12 into mitochondria, and the second is the conservation or reaction of MCM [38, 39].

MMAB

The *MMAB* gene is responsible for the cblB type of MMA. It is placed on chromosome 12q24.11 and contains 9 exons; this gene encodes cobalamin adenosyltransferase (ATR) with 250 amino acids. This transferase is essential for transferring the adenosyl group from cobalamin I to form AdoCbl [40].

MCEE

The *MCEE* gene is located on chromosome 2p13.3, consisting of 3 exons, and encodes 176 amino acids. This gene was the first identified cobalamin-related gene [41]. Methylmalonyl-CoA epimerase deficiency is an infrequent cause of persistent moderate MMA [42].

MMADHC

The cblD type is caused by a mutation(s) in the *MMADHC* gene located on chromosome 2q23.2, with 8 exons that encode 296 amino acids [43]. The product of this gene is involved in the conduction of cobalamin to two cobalamin-dependent enzymes in the mammalian cell: Methionine synthase and methylmalonyl CoA mutase [44].

MMACHC and homocystinuria

In the cblC type of MMA, the deficient gene is *MMACHC*. The *MMACHC* gene, on chromosome 1p34.1, contains 4 exons and encodes a polypeptide with 282 amino acids [45]. The mutation in this gene is combined with homocystinuria [28, 46].

The schematic diagram of genes responsible for methylmalonic acidemia disease, along with the details of exon and intron numbers, is shown in Figure 3.

The incidence of methylmalonic acidemia

The worldwide incidence of MMA is 1:50000-1:100000; however, the prevalence of MMA is higher in countries with the most consanguineous marriages, such as Turkey and Saudi Arabia [47]. For example, the rate of consanguineous marriage in Saudi Arabia is about 51%-56% of all marriages [48]. Iran is also a country where consanguineous marriage exceeds 35% [49]. A 10-year retrospective study revealed that about 80% of MMA patients in Iran are the result of consanguineous marriages [50], and the incidence of methylmalonic acid disease, among other metabolic diseases, is 9.12% in Iran [51]. There is no detailed investigation into MMA incidence in Iran, and the only previously published study is limited to a local survey. Indeed, a 9-year study in Isfahan province indicated that MMA is the most common form of metabolic disorder with an incidence rate of 1/10383 in live births [52]. So far, the incidence rate of this disease has not been addressed in other provinces of Iran.

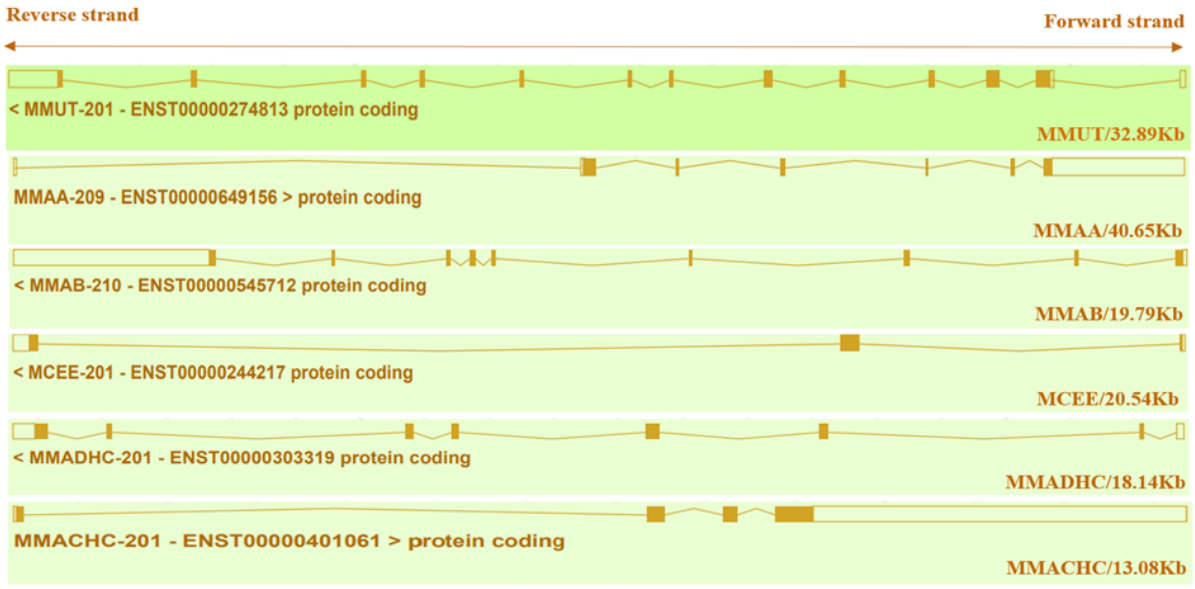

Figure 3. The exons (boxes) and introns (lines) associated with the genes involved in methylmalonic acidemia

Note: The blank region represents the untranslated region of an exon. The numbers represent gene size (adapted from Ensemble).

Clinical presentation of methylmalonic acidemia disease

Clinical manifestations of MMA are non-specific. MMA may exhibit at any age with chronic or acute symptoms. Some signs and symptoms are common, others are uncommon, and a few have only been described in isolated cases. In the classic and infantile-onset form of MMA, symptoms begin acutely on the second day of life and aggravate the general clinical condition; vomiting such as dehydration, weight loss, temperature instability, and nervous involvement with muscle hypotonia or hypertonia are mostly reported. Also, MMA can be characterized by lethargy, thrombocytopenia, neutropenia, severe ketoacidosis, and respiratory distress [12], and in some patients can lead to multiorgan failure, mental retardation, coma, and even death in the first year of life in these patients [53]. The disease symptoms do not present severely at birth, and the common symptoms of this disease, such as metabolic acidosis, hypoglycemia, hyperammonemia, and selective aminoacidemia, appear gradually from 2-3 days after birth [3].

Treatment of methylmalonic acidemia disease

The mortality rate in the first decade of 2000 was about 40% [13, 54], showing that MMA has a poor prognosis and, without treatment, can lead to long-term neurodevelopmental disorders [55]. There are numerous treatment options for MMA, including changes in diet to decrease the enzyme-substrate and administration of appropriate vitamins to accumulate the residual activity of the mutant enzyme [56]. The primary treatment for MMA is injecting the vitamin as hydroxocobalamin (OH-cbl) or cyanocobalamin (CN-cbl). Vitamin B12 injections can prevent symptoms in children with this type of MMA [57]. In addition, children with MMA can be treated with L-carnitine. It is a well-tolerated treatment with few side effects, including transient nausea, abdominal cramps, vomiting, and diarrhea. For some children with the most severe form of MMA, another treatment option is a kidney or liver transplant from a disease-free donor, which may reduce some of the symptoms. However, transplant surgery has serious risks and may not be appropriate for an affected child [58]. Therefore, early diagnosis and timely treatment may effectively help patients and prevent risky treatment procedures such as liver transplantation [55].

Materials and Methods

To study the worldwide distribution of MMA mutations, we utilized the Human Gene Mutation Database (HGMD) on August 30, 2023.

To investigate MMA mutations in Iran, PubMed, Google Scholar, and three Iranian databases were reviewed systematically to explore relevant articles in English and Persian. To compile these mutations, "advance search" was applied in the PubMed database using the keywords "MMA" and "methylmalonic acidemia" (in Title/Abstract) combined with

Table 3. Methylmalonic acidemia-causing mutations so far addressed in Iran

Gene	Mutation at Nucleotide Level	Mutation at Protein Level	Population	Reference
MUT	NM_000255: c.223A>T	p. Lys75X	Only in Iran	[10]
MUT	NM_000255: c.259G>A	p. Gly87Arg	Only in Iran	[62]
MUT	NM_000255: c.322C>T	p. Arg108Cys	North American Hispanic patients, black patients, Iran	[62-64]
MUT	NM_000255: c.454C>T	p. Arg152X	Iran, China	[62, 65]
MUT	NM_000255: c.469G>T	p. Val157Phe	Only in Iran	[66]
MUT	NM_000255: c.668A>G	p. Lys223Arg	Iran, Turkey	[10, 67]
MUT	NM_000255: c.693delC	p. Tyr231X	Only in Iran	[10]
MUT	NM_000255: c.808delG	p. Gly270X	Only in Iran	[10]
MUT	NM_000255: c.976A>G	p. Arg326Gly	Iran, Ukraine, China, India	[10, 59-61]
MUT	NM_000255: c.958G>A	p. Ala320Thr	Iran, China	[61, 66]
MUT	NM_000255: c.1055A>G	p. Gln352Arg	Only in Iran	[68]
MUT	NM_000255: c.1106G>A	p. Arg369His	Iran, China	[36, 62]
MUT	NM_000255: c.1137delT	p. Phe379Leu	Only in Iran	[66]
MUT	NM_000255: c.1874A>C	p. Asp625Ala	Iran, China, Switzerland,	[61, 66, 69]
MUT	NM_000255: c.2125-3C>G	-	Iran, China	[61, 70]
MMAA	NM-172250: c.295delG	p. Ala99Pro	Only in Iran	[66]
MMAA	NM-172250: c.672delA	-	Only in Iran	[66]
MMAA	NM_052845.4; c.749-750insGTTT	p. Ala252Vf*5	Only in Iran	[62]
MMAA	NM-172250: c.674delA	p. Asn225Met	Only in Iran	[71]
MMAA	NM-172250: c.1075C>T	p. Arg359Ter	Iran, Canada	[10, 72]
MMAB	NM_052845: c.197-1G>T	-	Iran, Canada	[10, 72]
MMAB	NM_052845: c.571C>T	p. Arg191Trp	Iran, Canada, Spain	[10, 73, 74]
MMAB	NM_052845.4; c.557G>A	p. Arg186Gln	Iran, Norway, India, Bahrain	[75-78]
MMAB	NM_052845.4; c.569G>A	p. Arg190His	Canada, Iran	[62, 73]

"Iran" (in Affiliation). In the Google Scholar database, we searched ["methylmalonic acidemia," mutation, and Iran]. To collect Persian articles, we checked the Magiran, CIVILICA, and SID databases by applying "methylmalonic acidemia" as a keyword (in search). The search in all five databases was performed on February 11, 2024. The systematic review research flow has been summarized in Figure 4.

Results

The frequencies of causative genes among MMA patients at the global level were *MUT* (64.14%), *MMACHC* (17.74%), *MMAA* (13.48%), *MMAB* (7.1%), *MMADHC* (2.9%), and *MCEE* (0.85%) (Figure 5). Therefore, the *MUT* gene is the most frequent, and the *MCEE* gene is the less frequent causative gene among MMA patients. This finding is somewhat in accord with the genes' size of the coding region.

Table 4. Types of mutations in the genes involved in methylmalonic acidemia disease (based on HGMD public version database)

Subtype	Gene	Mutation	Number of Mutations	%
Unresponsive to vitamin B12	*MMUT*	Missense/nonsense splice site Mutation small deletion Small insertion Small indel Gross deletion Gross insertions	246 30 55 36 5 2 2	64.14
cblA	*MMAA*	Missense/nonsense splice site Mutation Small deletion Small insertion Small indels Gross deletion	45 7 17 8 1 1	13.48
cblB	*MMAB*	Missense/nonsense splice site Mutation Regulatory Small deletion Small insertion Small indel	22 8 2 6 3 1	7.1
cblC	*MMACHC*	Missense/nonsense splice site Mutation small deletion Small insertion Small indel Gross deletion Gross insertion	56 8 24 10 1 4 1	17.74
cblD	*MMADHC*	Missense/nonsense small deletion Small insertion	10 4 3	2.9
MCEE	*MCEE*	Missense/nonsense Splice site mutation	4 1	0.85

Using the above-mentioned search strategy, 432 articles were extracted from Google Scholar, PubMed, Magiran, CIVILICA, and SID databases. After removing the duplicate and unrelated articles, 8 related articles were selected and reviewed to extract MMA pathogenic mutations in the Iranian population. In this systematic collection of MMA mutations in Iran, a total of 24 mutations have been reported, of which 11 mutations (45.8%) have not been reported in other populations yet and have been explicitly observed in Iran (Table 3). Also, the highest frequency of mutation is related to variant c.976A>G, which has been reported so far in four different geographical locations, including Ukraine [59], India [60], China [61], and Iran [10]. This mutation seems to be a recurrent mutation.

MMA is a genetically heterogeneous disorder due to mutations in *MUT*, *MMAA*, *MMAB*, *MMADHC*, *MMACHC*, and *MCEE* genes. In the HGMD database, 586 MMA-causative mutations have been reported in total, including 376 mutations in *MUT*, 79 mutations in *MMAA*, 42 mutations in *MMAB*, 104 mutations in *MMACHC*, 17 mutations in *MMADHC* and 5 mutations in *MCEE*.

Discussion

According to Table 4, the most causative mutations in MMA patients are located in the *MUT* gene (≈64%), while the lowest mutations belong to the *MCEE* gene (less than 1%). This worldwide distribution of MMA disease genes is also consistent with the Iranian population (Table 3), in which we can recognize 61% (11 out of 18) mutations in the *MUT* gene.

In the systematic collection of MMA disease mutations in Iran, a total of 24 mutations were reported, of which 11 mutations (45.8%) were observed exclusively in Iran and were not reported in other geographical regions. This issue shows the importance of having a database of genetic mutations at the national level.

It should be noted that in a collection of MSUD (Maple syrup urine disease) pathogenic mutations in Iran, 18 out of 24 collected mutations (75%) have been reported exclusively in Iran and not observed in other geographic areas [79]. This observation highlights the importance of having a nation-

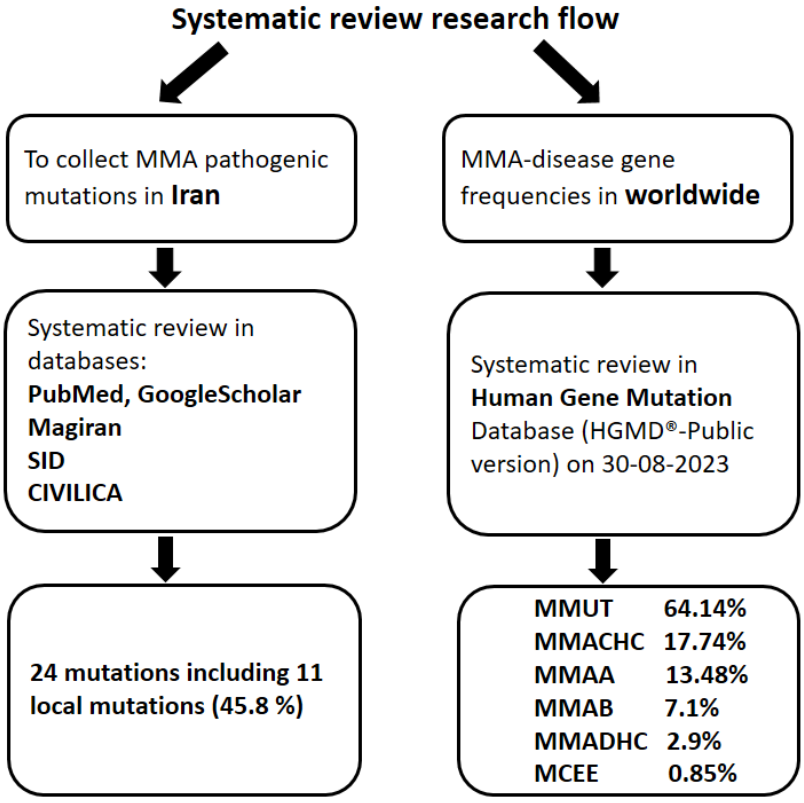

Figure 4. The systematic review research flow, utilized databases and results in the current study

wide genetic mutation database and attention that screening already known mutations is insufficient.

As early detection of MMA plays an essential role in preventing neurological symptoms, compiling MMA pathogenic mutations in the Iranian population facilitates early diagnosis and treatment and would also be helpful for at-risk families. These compiled pathogenic mutations can also be constructive for prenatal diagnosis and providing a local MMA mutation database.

Conclusion

Collection and recognition of MMA mutations in the Iranian population can be helpful for early diagnosis and treatment before the onset of neurological manifestations in neonates.

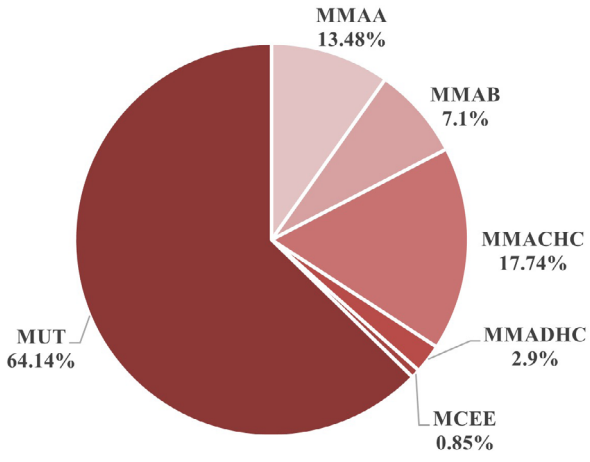

Figure 5. MMA disease gene frequencies at the global level
Note: The frequencies were extracted from the HGMD database.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contribution's

Conceptualization and supervision: Omid Jazayeri; Investigation and writing the original draft: Ghazaleh Malekizadeh; Review and editing: Omid Jazayer, Morteza Alijanpour and Majid Tafrihi; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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