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Whole exome sequencing in energy deficiency inborn errors of metabolism: A systematic review

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ABSTRACT

Broad biochemical complexity and frequent overlapping clinical symptoms of inborn errors of metabolism (IEM), especially in energy-deficient patients, make accurate diagnosis difficult. In recent years, whole exome sequencing (WES), a comprehensive protein coding genetic test, has been used to diagnose patients at the molecular level. This study aims to evaluate the potential of WES in diagnosing energy-deficient IEM patients with limited biochemical findings and to identify common symptoms patterns in reported cases. Articles were identified using a combination of search terms in online databases (Science Direct, PubMed Central and Wiley). English-language case reports citing WES in the diagnosis of energy-deficient IEM patients were reviewed. This systematic review was conducted and reported using the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' checklist. The quality and risk of bias were assessed using Joanna Briggs Institute critical appraisal tool. A total of 37 studies comprising of 54 case reports were included in this review. The median age of the patients was 0.4 years, with 55.6% being male and 44.4% being female. A total of 33 mutant genes were reported and they related to either metabolism or mitochondrial function. WES was able to identify mutations in 53 of 54 cases reported. The diagnosis of energy-deficient IEM patients is crucial, particularly given the challenging range of diverse clinical symptoms they present. The high accuracy of the WES technique appears to improve the diagnostic process. Further research defining more detailed guidelines is needed to engage with this rare set of genetic diseases.

1. Introduction

Inborn errors of metabolism (IEM) are a diverse set of disorders caused by genetic mutations which disrupt metabolic pathways [1]. Collectively, IEMs are rare disorders with an estimated global birth prevalence of 50.9 per 100,000 live births and accounting for a fatality rate of 0.4% of all child deaths per year [2].

IEM involves in various key pathways and organ systems, thus, resulting in a wide range of phenotypes [3]. From a pathological perspective, IEM can be clinically distinguished into three types: (i) energy deficiency, (ii) intoxication, and (iii) storage type. This study specifically focuses on the energy deficiency type of the disorder, which encompasses defects in carbohydrate metabolism, mitochondrial function, and fatty acid oxidation. These defects lead to common symptoms such as hypoglycemia, hyperlacticemia, severe generalized hypotonia and sudden infant death syndrome [4,5]. The onset of the symptoms can be at any age, with more severe forms appearing in early childhood [6].

The rationale for emphasizing the study on the energy deficiency type is due to the complexities involved in diagnosing IEM disorders associated with it. Interpreting biochemical screening results requires caution, as abnormalities detected are often nonspecific and may not be diagnostic on their own. For instance, elevated levels of lactic acid and pyruvate, while indicative of mitochondrial dysfunction in some cases, are not consistently sensitive or specific markers across all mitochondrial-related diseases. Nonetheless, when present, these elevations require serious consideration [7,8].

Current standard practises in the diagnosis of IEM, including of the energy deficiency type, require a series of basic laboratory

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investigations. These investigations are critical as they frequently provide the initial indications of IEM. To rule out an IEM, appropriate laboratory investigations should initially evaluate abnormalities in either small molecule metabolism (e.g., the mitochondrial energy metabolism) or organelle metabolism (e.g., lysosomes). However, due to the varied symptoms of IEM, no single straightforward diagnostic test is available.

Ideally, the diagnostic process usually involves components of newborn or high-risk screening, confirmation through specialized laboratory testing, and lifelong disease management. Basic metabolic assessments, usually conducted via blood and urine tests, provide initial screening but are not conclusive on their own [9]. On the other hand, advanced metabolic tests utilize biochemical reactions to identify specific metabolites, enzymes, or cofactors, employing techniques such as tandem mass spectrometry, gas chromatography–mass spectrometry [10,11], ultra/high-performance liquid chromatography [12], and enzymatic assays [13]. In other circumstances, more specialized investigations such as targeted molecular analyses, may be necessary for a definitive diagnosis [14]. Results from these laboratory investigations along with clinical symptoms, medical history, and family history, are usually sufficient to diagnose an IEM. Consequently, this allows the provision of early treatment – particularly in an emergency.

Even so, the proper identification of IEMs is challenging due to the inherent biochemical complexity as well as the broad and frequently overlapping clinical characteristics. Therefore, clinicians are utilizing whole exome sequencing (WES) more regularly in diagnosing patients at the molecular level. Unlike the traditional genomic approach, which relied on Sanger sequencing to sequence a single gene at a time [15], WES entails sequencing the entire protein-coding regions (exome regions) to uncover pathogenic mutations. WES is also reported for its high-throughput and cost-effectiveness in detecting disease-causing variants and identifying gene targets [16–18]. Utilizing massively parallel sequencing, WES generates millions of short read sequences more efficiently and affordably than traditional Sanger sequencing methods [17]. The turnaround time for WES ranges from 4 days for specific gene panels [19] to an average of 4 months for cases involving undefined disorders [20], depending on the extent of coverage.

Elements influencing the accuracy of disease diagnosis through WES include its comprehensive coverage, which analyzes approximately 1-2% of the entire genome [21], where the majority (85%) of disease-related mutations are found [22]. Moreover, precise detection capabilities enable the identification of various genetic variations, including single-nucleotide variants, deletions, insertions, and copy number variations [23]. Bioinformatic analyses further contribute by exploring connections between genes and diseases, integrating clinical information with curated databases, and incorporating findings from current research [17].

This review summarizes reported cases of energy deficient IEM patients diagnosed using WES. Our objective was to analyze the potential of WES in diagnosing these patients, especially in cases with limited biochemical test results. Additionally, we examined the patterns of the most common symptoms reported, aiming to facilitate early detection and subsequent management of these often-terminal conditions. Identifying energy-deficient IEM patients is essential, especially due to the complex and varied clinical symptoms they exhibit. Understanding and identifying these cases early on can be crucial for effective medical management.

2. Material and methods

2.1. Search database and strategy

This systematic review protocol was officially registered in PROSPERO under the registration number CRD42023476396. The registered protocol is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=476396. The articles were identified through searches in three databases: (Science Direct: https://www.sciencedirect.com/, PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/, and Wiley: https://onlinelibrary.wiley.com/), up until 5th July 2023. The combination of keywords '*inborn errors of metabolism*', '*whole exome sequencing*' and '*energy deficiency*' were used to search for the articles. Publications with accessible abstracts were first screened generally, and only research published in English was considered. Non-case report publications and duplicates were subsequently excluded.

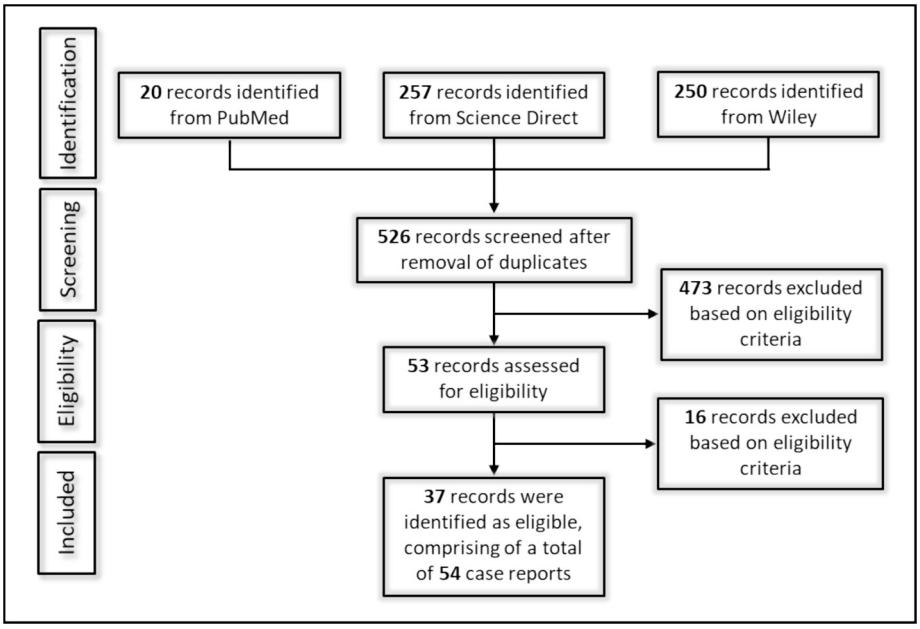

Fig. 1. PRISMA flow diagram of search for energy deficient IEM patients diagnosed using WES related literature. Appropriate literature was identified using three databases (Science Direct, PubMed, and Wiley). Duplicates were removed, the records were screened generally according to eligibility criteria (e.g., a case study in English language). The remaining records were further assessed for final selection (e.g., diagnosis was done using whole exome sequencing method).

Table 1a
Biochemical test of individual case reports.

No	Age & sex	Ethnicity	Region	Biochemical screening test							Reference / case study
				Biochemical routine finding	Acylcarnitine (DBS/P)	Carnitine (P/S)	Fatty acid (P/S)	Amino acid (P/S/U)	Organic acid (U)	Mitochondrial respiratory enzyme (CL)	
1	4 Years / Male	WC	EU	N/A	N/A	N/A	N/A	• Alanine, ↑ • Glutamate & glutamine were not tested	• Lactate, ↑	N/A	Rumping et al., 2023 [29] Study 1
2	3.8 Years / Female	AS	AS	N/A	N/A	N/A	N/A	• 3-methylhistidine, ↑	• 3-methylglutaconic acid, ↑ • Fumaric acid, glutaric acid, 3-methylglutaric acid, ↑ • 3-hydroxybutyric acid, trace	N/A	Al Tuwaijri et al., 2022 [30] Study 2
3	Newborn / Female	ND	EU	• Transaminases & CK, ↑	• Long chain AC, ↑ • Long-chain dicarboxylic acid	N/A	N/A	• Alanine, ↑↑	• Lactic acid, creatine, succinate, fumarate, 2-oxoglutarate, ↑	N/A	Bravo-Alonso et al., 2022 [31] Study 3
4	18 months / Female	ND	EU	• Hypoglycemia, ↑↑↑ • Liver enzymes, ↑ • Hypoglycorrhacia (CSF)	• Octanoyl-carnitine (C8), ↑	• Free carnitine acylcarnitine, ↓	N/A	• Glycine, ornithine, ↑ • Gly Plasma/CSF, Abn	N	N/A	Cani et al., 2022 [32] Study 4
5	4 years / Female	WC	NA	• Lactic acidosis • Anion gap ↑ • Lactate/Pyruvate ↑ • Lactate ↑ • Uric acid ↑ • Hypoalbuminemia ↓ • Liver function, N	• Acylcarnitine, N	• Carnitine, N	N/A	• Amino acids, N	• Lactic acidosis • Ketosis	• Complex IV, ↓	
6	8 years / Female	WC	NA	• Anion gap,↑ • Lactate/Pyruvate ↑	N/A	N/A	N/A	N/A	N/A	N/A	Friederich et al., 2020 [33] Study 5
7	4.3 years / Male	WC	NA	• Metabolic acidosis • Lactate, ↑ • Ketones, ↑ • CPK, ↑ • Myoglobin, ↑ • Transaminases, ↑	• Consistent with ketosis	N/A	N/A	• Glutamine, lysine, proline, alanine, methionine, tyrosine, ↑↑ • Citrulline, ↓ • Amino acids (CSF), N	• Lactate,ketones, dicarboxylic acid, ↑	N/A	
8	6 years / Male	ND	EU	• Creatinine kinase, ↑ • Plasma lactate, N	• Long chain C14:2, C16, C18:1, ↑	N/A	N/A	N/A	N/A	N	
9	18 years / Male	ND	EU	• Creatinine kinase, ↑ • Plasma lactate, N • Pyruvate, N • Liver transaminases, N	N	N/A	N/A	N	N	N	Schwantje et al., 2022 [34] Study 6
10	10 years / Female	ND	EU	• Creatinine kinase, N • Plasma lactate, N • Pyruvate, N • Liver transaminases, N	N	N/A	N/A	N	N	N/A	

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Table 1a (*continued*)

No	Age & sex	Ethnicity	Region	Biochemical screening test							Reference / case study
				Biochemical routine finding	Acylcarnitine (DBS/P)	Carnitine (P/S)	Fatty acid (P/S)	Amino acid (P/S/U)	Organic acid (U)	Mitochondrial respiratory enzyme (CL)	
11	Newborn / Female	HL	NA	• Liver transaminases, ↑ • Lactate dehidrogenase, ↑ • Blood ammonia, ↑	N/A	N/A	N/A	N/A	N/A	• Activities of multiple complexes, ↓	Ni et al., 2021 [35] Study 7
12	Newborn / Male	ND	NA	• Lactic acidosis	ABN	ABN	N/A	ABN	ABN	N/A	Morales et al., 2021 [36] Study 8
13	2 months / Male	ND	AS	• Respiratory alkalosis with metabolic alkalosis	N	N	N	N	N	N/A	Wen et al., 2022 [37] Study 9
14	Newborn / Female	AS	AS	N/A	N/A	N/A	N/A	N/A	• Presentation of 3-methylcrotonylglycine	N/A	Shao et al., 2021 [38] Study 10
15	5.5 years / Male	WC	EU	• Biochemical parameter, N • Creatine kinase, N • Serum ammonia, N • Lactic acid, N • Pyruvic, N	N	N/A	N	N	N	N/A	Uzun et al., 2021 [39] Study 11
16	5 years / Female	ND	NA	N/A	N/A	N/A	N/A	• S- sulphocysteine, ↑↑↑ • alpha-amino-adipic semialdehyde, ↑↑↑	N/A	N/A	Lee et al., 2021 [40] Study 12
17	8 months / Female	AS	AS	• Hyperammonaemia, ↑ • Metabolic acidosis, ↑↑↑ • Pyruvic acid, N • Lactic acid, N • Creatine phosphokinase, N • Hypoglycemia	N	N/A	N/A	N	• Glutaric acid, ↑	N/A	Heidari et al., 2020 [41] Study 13
18	2 Month / Male	AS	AS	N/A	N/A	N/A	N/A	N	N	N/A	Park et al., 2020 [42] Study 14
19	Newborn / Female	WC	NA	N/A	N/A	N/A	N/A	N/A	N/A	• Complex I & IV activities, ↓ • Added bands of F1 subunit of Complex V	Bennett et al., 2020 [43] Study 15
20	12 years / Female	ND	NA	• CSF protein, ↑	N	N/A	N/A	• Valine and lysine, ↑	N/A	N/A	Wilton et al., 2020 [44] Study 16
21	Newborn / Female	ND	NA	N/A	↑	N/A	N/A	ABN	ABN	• Complex IV activity, ↓	Mardian et al., 2020 [45] Study 17

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Table 1a (*continued*)

No	Age & sex	Ethnicity	Region	Biochemical screening test							Reference / case study
				Biochemical routine finding	Acylcarnitine (DBS/P)	Carnitine (P/S)	Fatty acid (P/S)	Amino acid (P/S/U)	Organic acid (U)	Mitochondrial respiratory enzyme (CL)	
22	6 months / Male	AS	AS	• Metabolic acidosis, ↑↑↑	N/A	N/A	N/A	• Alanine, ↑ • Methionine, ↓	• Ketones, ↑ • Lactate, ↑ • dicarboxylic aciduria, ↑ • 3-OH propionic aciduria, ↑ • Krebs cycle metabolites, ↑	N/A	Hershkovitz et al., 2019 [46] Study 18
23	11 years / Male	AS	AS	• Metabolic studies, N	N/A	N/A	N/A	N	N	• Native PDH enzyme, ↓ • DCA activated PDH, N • Pyruvate carboxylase, N	Nimmo et al., 2019 [47] Study 19
24	9 years / Male	AS	AS	N/A	N/A	N/A	N/A	N/A	N/A	• Native PDH enzyme, ↓ • DCA activated PDH, N • Pyruvate carboxylase, N	
25	11 years / Male	AS	AS	• Lactic acidemia, ↑ • Lactate to pyruvate ratios, ↑	↑	N	N/A	N	N	N/A	Gustafson et al., 2019 [48] Study 20
26	2 months / Male	ND	AS	• Serum ammonia, N • Lactate, N	N	N/A	N/A	N	N	N/A	Rostami et al., 2020 [49] Study 21
27	13 months / Male	ND	AS	N	N	N	N	N	N	N	
28	7 years / Male	AS	AS	• Lactate, ↑ • Pyruvate, ↑	N/A	N/A	N/A	N/A	N/A	N/A	Conboy et al., 2018 [50] Study 22
29	4 months / Male	WC	NA	• Ammonia, ↑ • Plasma lactate, ↑	N	N/A	N/A	N	N	N/A	Shayota et al., 2019 [51] Study 23
30	3 months / Female	AS	AS	N/A	N/A	N/A	N/A	N/A	N/A	• OXPHOS activity, N	Sharkia et al., 2019 [52] Study 24
31	4 months / Female	AS	AS	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
32	7 months / Female	HL	NA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
33	Newborn / Male	WC	NA	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
34	Newborn / Male	WC	NA	N/A	N/A	N/A	N/A	N/A	N/A	• OXPHOS activity, N	
35	3 months / Female	WC	EU	N/A	N/A	N/A	N/A	N/A	N/A	• Complex I-III, ↓	
36	2 months / Male	AF	EU	N/A	N/A	N/A	N/A	N/A	N/A	N/A	

(*continued on next page*)

Table 1a (*continued*)

No	Age & sex	Ethnicity	Region	Biochemical screening test							Reference / case study
				Biochemical routine finding	Acylcarnitine (DBS/P)	Carnitine (P/S)	Fatty acid (P/S)	Amino acid (P/S/U)	Organic acid (U)	Mitochondrial respiratory enzyme (CL)	
37	1 year / Male	AF	EU	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
38	Newborn / Male	AS	AS	• Ammonia, ↑	N/A	N/A	N/A	• Citrulline, ↓ • Alanine, ↑	• Lactate, ↑ • Ketone bodies, ↑	N/A	Zhang et al., 2018 [53] Study 25
39	Newborn / Female	AS	AS	• Hyperammonemia	N/A	N/A	N/A	• Citrulline, ↓	N/A	N/A	
40	Newborn / Male	WC	NA	• Metabolic acidosis • Lactate, ↑ • Ammonia, N	• C5:1, ↑	N/A	N/A	• Alanine, ↑↑↑	• Lactate, ↑↑↑ • Pyruvate, ↑↑↑ • Ketones, ↑↑↑ • Branched-chain ketoacids, ↑↑↑ • 3-methylglutaconic acid, ↑↑↑	N/A	Bedoyan et al., 2017 [54] Study 26
41	2 months / Male	HL	NA	• Hyperlactatemia • Pyruvate, ↑	N	N/A	N/A	• Alanine, ↑ • Proline, ↑	• Lactate, ↑ • Succinate, ↑ • Fumarate, ↑ • 2-hydroxiglutarate, ↑	N/A	Stowe et al., 2018 [55] Study 27
42	9 months / Male	AS	EU	N/A	N/A	N/A	N/A	• Suggested proximal urea cycle defect.	• Prominent TCA cycle metabolite	N/A	Santra et al., 2016 [56] Study 28
43	6 months / Male	AF	NA	• Basic chemistry, N • Serum lactate, N • Serum alpha-fetoprotein, N • Liver function test, N	N	N/A	N/A	N	N	N/A	Sadat et al., 2016) [57] Study 29
44	12 years / Female	ND	NA	• AFP levels, ↑↑↑	N/A	N/A	N/A	N	N	N/A	Blackburn et al., 2016 [58] Study 30
45	3 months / Female	WC	NA	N	N	N	N	N	N/A	N/A	Soler-Alfonso et al., 2015 [59] Study 31
46	Newborn / Male	ND	NA	N/A	N/A	• Free carnitine, N • Long-chain species, N • Acetylcarnitine, ↑	N/A	N/A	N/A	N/A	Leslie et al., 2016 [60] Study 32
47	7 years / Male	WC	EU	• Glucose, N • Insulin, N • Lactate, N	N/A	N/A	N/A	N/A	N/A	N/A	Szymańska et al., 2015 [61] Study 33

(*continued on next page*)

Table 1a (*continued*)

No	Age & sex	Ethnicity	Region	Biochemical screening test							Reference / case study
				Biochemical routine finding	Acylcarnitine (DBS/P)	Carnitine (P/S)	Fatty acid (P/S)	Amino acid (P/S/U)	Organic acid (U)	Mitochondrial respiratory enzyme (CL)	
48	4 months / Male	AS	EU	• Plasma lactate, ↑ • Uric acid, N	N	N/A	N	N	N	• Complex I and II activity, ↓ • Fibroblast oxidative phosphory-lation, N	
49	3 months / Female	AS	EU	• Plasma & CSF lactate, N	N	N/A	• C24 fatty acids, ↑ • Phytanic acid, ↑	N	N	N/A	Kevelam et al., 2015 [62] Study 34
50	4.5 months / Male	FN	EU	• Plasma & CSF lactate, N	ABN	N/A	N	N	N	• Respiratory chain complex I (muscle biopsy), N • Respiratory chain complex II (muscle biopsy, N • Respiratory chain complex IV, (muscle biopsy), N	
51	7 months / Male	AS	EU	• Blood lactate, ↑	N	N/A	N/A	N	N	• Complex I, ↓ • Combined complexes I + III, ↓ • Complexes II and III, ↓	Reuter et al., 2014 [63] Study 35
52	5 months / Female	HL	EU	• Histochemistry, N	N/A	N/A	N/A	N/A	N/A	• Combined complex I and III, ↓ • Complex I (culture fibroblasts), ↓	Delmiro et al., 2013 [64] Study 36
53	3 months / Female	ND	EU	• Lactic acidemia	N/A	N/A	N/A	N/A	N/A	• Complex IV, ↓	Baruffini et al., 2013 [65] Study 37
54	5 months / Female	ND	EU	• Lactic acidemia	N/A	N/A	N/A	N/A	N/A	• Complex IV, ↓	

Legend
- Ethnicity: WC (White/Caucasian); AS (Asian); AF (African); HL (Hispanic/Latino); others (E.g. FN: First nation) & ND (Not determined)
- Region: EU (Europe); AS (Asia); NA (North America); OC (Oceania); AF (Africa)
- Biochemical Screening Tests:
  - o *Type of changes: arrow up* (↑) – *increased, arrow down* (↓) – *decreased, N – normal*
  - o *Level of changes: One arrow* (↑) – *mild, two arrows* (↑↑) – *moderate, three arrows* (↑↑↑) – *severe*
  - o *Sample type: DBS – dried blood spot, P – plasma, S – serum, U – urine, CL – cell lysate*
  - o *ABN – Abnormal, N/A – not available*

2.2. Eligibility criteria

Cases selected were patients diagnosed and compliant with the classification of the energy deficient IEM pathophysiologic type. Specifically classified as '*category 2, group 2*': diseases of primary biochemical defects/disorders involving primary energy metabolism (Supplementary File 1) [24]. The symptoms included deficiency in energy production or utilization, and also of a membrane transporter of metabolic intermediates. Molecular diagnosis was made using the whole exome sequencing method. Cases using other sequencing methods for molecular diagnosis such as sanger sequencing (apart from confirmation test) or targeted exome sequencing were omitted.

2.3. Study selection, data mining and management

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA: http://prisma-statement.org/prismastatement/flowdiagram.aspx) checklist guideline was followed in performing and reporting this systematic review (Supplementary File 2) [25]. Titles and abstracts were examined for potential qualifying studies and assessed independently by two authors (FDAN and AO). All data were extracted independently using standardized data collection forms. The tabulated results included demographic background of age, sex, and ethnicity; presenting symptoms; biochemical screening test and results (variants, gene and disease). All reported data were also reviewed for accuracy, and any differences that arose during the process were addressed by discussion and by a third author (BK) when required. Missing data was classified as "Not Available (N/A)" in this review.

2.4. Quality assessment

The validity of the selected case reports was assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for case report [26]. The quality of the study methodology and any risk of bias potential were evaluated with an 8-questions checklist. Each included study was assessed independently by three review authors (FDAN, OA, and BK). A majority vote was employed to resolve disagreements along these processes (e.g., contradictions in appraisal judgments).

2.5. Data analysis

Descriptive statistical analysis was performed on patients' demographic and some general symptom information in all included studies. Data was analysed using IBM SPSS Statistics version 22 [27]. The findings were expressed as a median (range) with statistical significance set at $p < 0.05$. Sensitivity and specificity value also were evaluated using an online diagnostic test evaluation calculator [28]. Missing data were not included in statistical analysis and were classified as unreported data. Screening of biochemical tests was evaluated, and patients must have undergone at least one of the following tests; (i) Plasma amino acid; (ii) Organic acid; (iii) Newborn screening; (iv) Plasma acylcarnitine; and (v) Mitochondrial respiratory chain enzyme assay.

3. Results

3.1. Study characteristics

The initial general search of literature yielded 526 articles using the search keywords. Following screening of titles and abstracts, the list of articles was filtered by removing duplicate and irrelevant articles. The study identification process is illustrated in the PRISMA flow diagram (Fig. 1). After a thorough article selection, 53 case reports were assessed for eligibility, with 37 ultimately being included in this review. Several case reports contained more than one individual case, resulting in 54 documented cases in this review, as shown in Tables 1a and 1b.

3.2. Quality assessment of study validity

The quality and risk of bias were assessed in each of the included studies. The total outcome of its major component is demonstrated in Table 2. A total of 19 % of the case reports scored "yes" for all of the checklist questions. 78 % of the studies scored at least 5 out of the 8 questions. Overall, the included studies mostly ranged from moderate to high quality case report.

4. Discussion

4.1. Demographics and general clinical symptoms

Demographic data from the 54 case reports showed patients have a median age of 0.4 years (ranged from 0 to 18 years) with 55.6 % of the population being male and 44.4 % female. Asians (31.5 %) had the largest prevalence compared to other races (White/Caucasian: 25.9 %; African: 5.6 %; Hispanic/Latino: 5.6 %; others: 1.9 %) with 29.6 % of unreported ethnicity. Region classification was analysed based on the origin of the reported cases, with Europe, North America, and Asia accounting for 35.2 %, 35.2 %, and 29.6 %, respectively.

IEM patients displayed a wide spectrum of clinical symptoms. Neurological, hepatic, and cardiac defects were only some of the clinical manifestations [66]. This review extracted information on a wide range of presenting symptoms, which were presented in Table 1b. Four common general symptoms related to energy deficiency indication shared by patients had been analysed. These were muscle weakness [HP:0001324], hypotonia [HP:0001252], hypoglycaemia [HP:0001943], and seizures [HP:0001250]. Results showed that there was no statistical significance obtained, implying that these symptoms may or may not be relevant to an energy deficiency illness. More research with a larger group of cases may be needed to better understand the connection, if any, between these symptoms and the illness (Supplementary File 3). The most prevalent symptoms reported in energy deficiency IEM patients include hypoglycemia, hyperlacticaemia, severe generalized hypotonia as well as sudden infant death syndrome [5].

4.2. Diagnostics approaches

In the diagnosis of IEM patients, various approaches and methods were used by clinicians such as biochemical, enzymatic, and molecular testing. Biochemical diagnosis is based on the determination of abnormal levels of biochemical substrate and/or product, which can be performed with urine organic acid analysis, plasma amino acid analysis, and specific analyte testing. However, this approach has its own limitation whereby some tests involved invasive procedures, such as liver biopsy and skin biopsy, for hepatic glycogen storage disease and fatty acid oxidation investigations, respectively [14].

In terms of enzymatic diagnostics, direct testing of their function can be conducted and therefore can help to predict the severity of some disorders. However, due to the specific catalytic mechanisms of these methods, which are unique to their respective substrates, the testing process operates at a low throughput. Additionally, they are restricted to only one type of enzyme for each substrate, and their implementation involves laborious and expensive techniques for substrate synthesis. Alternatively, molecular sequencing of the putative abnormal genes can be informative when neither biochemical nor enzymatic tests can confirm or rule out an IEM. In such instances, clinicians may need to rely on the patient's clinical progression if any of these tests were unable to conclusively confirm the disorder [67].

Our analysis revealed that biochemical tests conducted prior to WES demonstrated moderate sensitivity, indicating their ability to accurately identify positive cases. However, these tests were less specific, suggesting a lack of precision in distinguishing true negative cases and potentially leading to higher false positive rates. Additionally, when assessed using receiver operating characteristic curve (ROC) analysis,

Table 1b
Clinical presentations and genetic tests of individual case reports.

No	Age & sex	Clinical symptoms	Other diagnostic marker	Variants	Gene	Disease	Reference / case study
1	4 Years / Male	• Developmental delay • Epilepsy with tonic clonic seizures	• MRS (Brain): Glutamate, ↑	c.1382 A > T p.(His461Leu)	*GLS*	Glutaminase disorder	Rumping et al., 2023 [29] Study 1
2	3.8 Years / Female	• Cardiomyopathy • Global developmental delay • Chest infection • Seizures	• MRI, N • MRI (Brain): extensive high T2 signal intensity and restricted diffusion in both cerebral hemispheres • EEG, N	c.159del p.(Phe54Leufs*5)	*DNAJC19*	3-methylglutaconic aciduria type V	Al Tuwaijri et al., 2022 [30] Study 2
3	Newborn / Female	• Hypotonia • Lethargy • Hypoglycemia • Metabolic decompensation • Hyperammonemia • Dilated cardiomyopathy	• Anatomopathological study: myocardial infarction	c.157 A > C p.(Thr53Pro) c.284C > T p.(Ala95Val)	*PPCDC*	Phosphopantothenoylcysteine decarboxylase deficiency	Bravo-Alonso et al., 2022 [31] Study 3
4	18 months / Female	• Lethargy • Feeding difficulties • Vomiting • Seizure	• Urinary dicarboxylic acids and hexanoylglycine, ↑ • MRI (Brain): cerebral edema • Lysosomal enzymes, N	c.244dupT p.(Trp821Leufs*23) c.985 A > G p.(Lys329Glu)	*ACADM*	Medium- chain acyl- coenzyme A dehydrogenase deficiency	Cani et al., 2022 [32] Study 4
5	4 years / Female	• Comatose • Lactic acidosis • Multiple organ failure • Hypotonic • Neurostorming episodes	• MRI (Brain), T2 prolongation and diffusion restriction • Magnet resonance spectroscopy (Brain): large lactate peak with a depressed *N*-acetylaspartate	c.637G > A p.(Glu213Lys)	*SQOR*	Leigh disease	Friederich et al., 2020 [33] Study 5
6	8 years / Female	• Fever, nausea, vomiting • Comatose with apnea requiring intubation	• MRI (Brain): diffusion of left cortex and right corted, restricted diffusion of caudate nuclei and putamina. • Magnet resonance spectroscopy (Right basal ganglia): large lactate inverted doublet, choline ↑, *N*-acetylaspartate ↓	c.637G > A p.(Glu213Lys)	*SQOR*	Leigh disease	
7	4.3 years / Male	• Encephalopathic • Hypoglycemia, ↑ • Hyperammonemia, ↑	• MRI (Brain): lesions of corpus callosum, mild encephalitis/encephalopathy with reversible splenial lesions (MERS)	c.446delT p.(Leu149Argfs*18)	*SQOR*	Leigh disease	
8	6 years / Male	• Muscle weakness • Hypotonia • Abnormal and deteriorating gait • Respiratory insufficiency	N/A	c.209 + 1G > C p.(Ala37AspfsX5) c.397 A > G p.(Thr133Ala)	*HADHB*	Mitochondrial trifunctional protein (MTP) deficiency	Schwantje et al., 2022 [34] Study 6
9	18 years / Male	• Muscle weakness	• No presence of myoglobinuria MRI brain and CSF fluid analysis, N	c.248C > G p.(Ala83Gly) c.694G > A p.(Ala232Thr)	*HADHB*	MTP deficiency	
10	10 years / Female	• Muscle weakness • Exercise intolerance • Leg pain • Developed obesity at early age	N/A	c.397 A > G p.(Thr133Ala)	*HADHB*	MTP deficiency	
11	Newborn / Female	• Persistent pulmonary hypertension • Lactic acidosis	• Brain ultrasound: colpocephaly and absence of the corpus callosum	c.949G > T p.(Gly317Cys)	*EARS2*	Combined oxidative phosphorylation deficiency, subtype	Ni et al., 2021 [35] Study 7

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Table 1b (*continued*)

No	Age & sex	Clinical symptoms	Other diagnostic marker	Variants	Gene	Disease	Reference / case study
		• Bradycardia • Respiratory depression					
12	Newborn / Male	• Hypoglycemia • Profound neonatal lactic and metabolic acidosis • Renal tubulopathy • Sensorineural hearing loss (SNHL)	N/A	c.3208_3210delGAG p.(Arg1072del)	*PHKA2*	Glycogen storage disease IX	Morales et al., 2021 [36] Study 8
13	2 months / Male	• Recurrent vomiting and persistent seizure • Hypotonia • Dysphagia • Congenital heart disease • Neurological development delay	• Thyroid function test: T3, T4, TSH, free T3 and free T4; ↓ • Serum total 25-OH indicated vitamin D deficiency	c.357C > G p.(Asp119Glu) c.611C > T p.(Ala204Val)	*NDUFAF5*	Leigh syndrome	Wen et al., 2022 [37] Study 9
14	Newborn / Female	• Seizure • Encephalopathy • Hypotonia • Progressive myopia • Global developmental delay • Intellectual disability • Poor feeding • Mild splenomegaly • Obstructive sleep apnoea	N/A	c.920 T > G p.(Leu307Arg) c.794 T > G p.(Leu265Arg)	*GNB5L & GNB5S*	multiple ultra-rare genetic syndromes	Shao et al., 2021 [38] Study 10
15	5.5 years / Male	• Fatigue • Difficulty in climbing stairs • Mild kyphoscoliosis	• Vitamin B12, N	c.1390G > A p.(Gly464Ser)	*HADHB*	Mitochondrial trifunctional protein deficiency	Uzun et al., 2021 [39] Study 11
16	5 years / Female	• Quadriplegic cerebral palsy • Severe global developmental delay • Microcephaly • Cystic encephalomalacia • Epilepsy • Bilateral ectopia lentis • Recurrent urinary tract infections • Hypertonia	N/A	c.493 T > C p.(Trp165Arg) c.539_540delAA p.(K180RfsX31)	*MOCS2*	Molybdenum cofactor deficiency	Lee et al., 2021 [40] Study 12
17	8 months / Female	• Upper respiratory symptoms • Vomiting • Tachypnoea • Seizure • Poor feeding • Decreased consciousness • Hepatomegaly	N/A	c.266G > A p.(Gly89Asp)	*HMGCS2*	HMG-CoA synthase deficiency	Heidari et al., 2020 [41] Study 13
18	2 Month / Male	• Hypotonia • Cyanosis • Abnormal eye movements • Psychomotor retardation • Intractable seizures manifesting with cyanotic episodes • Diffuse cerebral atrophy and bilateral optic atrophy without cerebellar atrophy	N/A	c.1179G > A p.(Met393Ile) c.1343G > C p.(Cys448Ser)	*ACO2*	Infantile cerebellarretinal degeneration	Park et al., 2020 [42] Study 14

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Table 1b (*continued*)

No	Age & sex	Clinical symptoms	Other diagnostic marker	Variants	Gene	Disease	Reference / case study
19	Newborn / Female	• Severe lactic acidosis	N/A	c.994C > T p.(Arg332*)	*MTFMT*	Mitochondrial methionyl-tRNA formyltransferase deficiency	Bennett et al., 2020 [43] Study 15
20	12 years / Female	• Seizures • Pneumonia • Ataxia • Stiffened gait	N/A	c.161 + 1G > A c.386G > C p.(Arg129Pro)	*MICU1*	Mitochondrial calcium uniporter 1 deficiency	Wilton et al., 2020 [44] Study 16
21	Newborn / Female	• Mild hypoglycaemia • Lactic acidosis	N/A	Not detected	–	Normal genotype	Mardian et al., 2020 [45] Study 17
22	6 months / Male	• Hernia • Flu-like symptoms • Tachycardia • Hypotension • Hypothermia • Lactic acidosis • Dilated cardiomyopathy (DCM)	N/A	c.344 A > C p.(His115Pro)	*TUFM*	Autosomal recessive combined oxidative phosphorylation deficiency 4	Hershkovitz et al., 2019 [46] Study 18
23	11 years / Male	• Bilateral cataracts • Developmental delays • Hypotonia	N/A	c.2282C > T p.(Pro761Leu)	*LONP1*	CODAS syndrome	Nimmo et al., 2019 [47] Study 19
24	9 years / Male	• Hypotonia • Difficulty swallowing • Seizures	N/A	c.2282C > T p.(Pro761Leu)	*LONP1*	CODAS syndrome	
25	11 years / Male	• Speech delay • Learning difficulties • Severe aplastic anemia • Developmental delay • Congenital hypotonia • Hearing loss	N/A	c.79G > A p.(Glu27Lys)	*SSBP1*	Severe and progressive mitochondrial disease manifestations across the full Pearson, Kearns-Sayre, and Leigh syndromes spectrum	Gustafson et al., 2019 [48] Study 20
26	2 months / Male	• First child from consanguineous marriage • Recurrent seizures • Neurologic regression • Developmental delayed • Abnormal facies	N/A	c.92 > T p.(Pro31Leu	*SLC6A8*	Creatine transporter deficiency	Rostami et al., 2020 [49] Study 21
27	13 months / Male	• Second child of consanguineous parents • Hypotonic • No history of seizure	• Brain MRI, N	c.134G > A p.(Trp45*)	*GAMT*	Guanidinoacetate methyltransferasedeficiency	
28	7 years / Male	• Developmental delay • Recurrent hemiplegia • Facial and ocular involvement	N/A	c.150_153delCGGC p.(Arg52fs)	*TTC19*	Mitochondrial complex III deficiency, nuclear type 2 (MC3DN2)	Conboy et al., 2018 [50] Study 22
29	4 months / Male	• Hypotonia • Vomiting • Diarrhoea	N/A	c.538 A > G p.(Thr180Ala)	*ECSH1*	Short chain enoyl-CoA hydratase (SCEH) deficiency	Shayota et al., 2019 [51] Study 23

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Table 1b (*continued*)

No	Age & sex	Clinical symptoms	Other diagnostic marker	Variants	Gene	Disease	Reference / case study
		• Failure to thrive		c.444G > T p.(Met14Ile)			
30	3 months / Female	• Ataxia • Hypotonia • Optic atrophy • Strabismus • Global developmental delay • Mental retardation • Microcephaly • Scoliosis	N/A	c.336C > G p.(Ser112Arg)	*ACO2*	*ACO2* deficiency	
31	4 months / Female	• Ataxia • Hypotonia • Seizures • Optic atrophy • Strabismus • Global developmental delay • Mental retardation • Microcephaly • Scoliosis	N/A	c.336C > G p.(Ser112Arg)	*ACO2*	*ACO2* deficiency	
32	7 months / Female	• Ataxia • Hypotonia • Optic atrophy • Strabismus • Global developmental delay • Mental retardation • Scoliosis	N/A	c.260C > T p.(Ser87Leu) c.685-I_685delinsAA p.(Val229Met)	*ACO2*	*ACO2* deficiency	Sharkia et al., 2019 [52] Study 24
33	Newborn / Male	• Hypotonia • Seizures • Optic atrophy • Strabismus • Global developmental delay • Mental retardation • Scoliosis	N/A	c.1181G > A p.(Gly394Glu) c.1722G > A p.(Asp574X)	*ACO2*	*ACO2* deficiency	
34	Newborn / Male	• Ataxia • Hypotonia • Seizures • Optic atrophy • Global developmental delay • Mental retardation • Microcephaly	N/A	c.172C > T p.(Arg58X) c.590 A > G p.(Asn197Ser)	*ACO2*	*ACO2* deficiency	
35	3 months / Female	• Hypotonia • Seizures • Optic atrophy • Strabismus • Global developmental delay • Mental retardation • Microcephaly	N/A	c.1859G > A p.(Gly620Asp) c.2048G > A p.(Gly683Val)	*ACO2*	*ACO2* deficiency	

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Table 1b (*continued*)

No	Age & sex	Clinical symptoms	Other diagnostic marker	Variants	Gene	Disease	Reference / case study
36	2 months / Male	• Ataxia • Hypotonia • Seizures • Optic atrophy • Strabismus • Global developmental delay • Mental retardation	N/A	c.1787 A > G p.(His596Arg) c.2050C > T p.(Arg684Trp)	*ACO2*	*ACO2* deficiency	
37	1 year / Male	• Ataxia • Hypotonia • Seizures • Global developmental delay • Mental retardation	N/A	c.1787 A > G p.(His596Arg) c.2050C > T p.(Arg684Trp)	*ACO2*	*ACO2* deficiency	
38	Newborn / Male	• Poor feeding • Frequent vomiting • Seizures	N/A	c.2537C > T p.(Pro846Leu) c.3443 T > A p.(Met1148Lys)	*CPS1*	Carbamoyl phosphate synthetase 1 deficiency (CPS1D)	Zhang et al., 2018 [53] Study 25
39	Newborn / Female	• Difficulty in feeding • Drowsiness • Groaning • Tachypnoea • Hyper myotonia • Coma	• CSF and CT scan, N	c.1799G > A p.(Cys600Tyr) c.4088_4099del p.(Leu 1363_Ile1366del)	*CPS1*	CPS1D	
40	Newborn / Male	• Mild jaundice • Decreased overall tone and activity	N/A	c.836 T > C p.(Phe279Ser) c.8C > A p.(Ala3Asp)	*ECHS1*	SCEH	Bedoyan et al., 2017 [54] Study 26
41	2 months / Male	• Intractable vomiting • Irritability • Seizures • Severe lactic acidosis • Non-consanguineous child • No presence of organomegaly	N/A	c.212C > T p.(Ser71Phe) c.539 T > C p.(Leu180Ser)	*LIPT1*	Lipoyl transferase 1 deficiency	Stowe et al., 2018 [55] Study 27
42	9 months / Male	• Persistent diarrhoea • Vomiting • Encephalopathy • Acute liver failure • Hyperlactatemia	• Orotic acid, ↑	c.1319_1330delGTGTCCCTCTAG p.(GlyValproLeuVal123Val)	*PCK1*	Phosphoenolpyruvate carboxykinase deficiency	Santra et al., 2016 [56] Study 28
43	6 months / Male	• Ataxia • Hypotonia • Global developmental delay • Dysmorphic facial features • Myoclonic jerks • Sensorineural hearing loss bilaterally • Cog-wheel eye saccades	N/A	c.2135C > T p.(Pro712Leu) c.1819C > T p.(Arg607Cys)	*ACO2*	Mitochondrial Aconitase Deficiency	Sadat et al., 2016 [57] Study 29
44	12 years / Female	• Hepatosplenomegaly • Abdominal bloating • Vomiting	N/A	c.424 A > G p,(Arg142Gly)	*FAH*	Tyrosinemia Type I	Blackburn et al., 2016 [58] Study 30

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Table 1b (*continued*)

No	Age & sex	Clinical symptoms	Other diagnostic marker	Variants	Gene	Disease	Reference / case study
45	3 months / Female	• Nystagmus • Muscle weakness	N/A	c.517 + 1G > A c.410C > T p,(Ala137Val)	*HIBCH*	Leigh syndrome	Soler-Alfonso et al., 2015 [59] Study 31
46	Newborn / Male	• Lactic acidosis	N/A	c.187G > T p.(Glu63*) c.941 T > C p.(Leu314Pro).	*ACAD9*	Complex I deficiency	Leslie et al., 2016 [60] Study 32
47	7 years / Male	• Random, asymptomatic hypoglycemia with ketonuria	• Poor response to glucagon during Glucose Challenge Test	c.1720 T > C p.(Phe574Leu)	*GYS2*	Glycogen storage disease 0	Szymańska et al., 2015 [61] Study 33
48	4 months / Male	• Microcephaly • Seizures • Hypotonia • Feeding difficulties • Vomiting • Cataract	• Transferin iso electric focusing, N • Mitochondria DNA, N	c.264-607_295 + 1267del	*ITPA*	Inosine triphosphate pyrophosphatase (ITPase) deficiency	Kevelam et al., 2015 [62] Study 34
49	3 months / Female	• Microcephaly • Seizures • Developmental delay • Hypotonia • Respiratory infection	• Transferrin IEF, N	c.452G > A p,(Trp151*)	*ITPA*	ITPase deficiency	
50	4.5 months / Male	• Microcephaly • Seizures • Developmental delay • Hypotonia • Respiratory infection • Hypotelorism • Myopia • Astigmatism	• Transferrin IEF, N	c.532C > T p.(Arg178Cys)	*ITPA*	ITPase deficiency	
51	7 months / Male	• Psychomotor delay • Generalized muscular hypotonia • Convergent N/Astrabismus. • Feeding difficulties • Bilateral optic nerve atrophy • Blindness	• Brain MRI - symmetric signal abnormalities of the basal ganglia and reduced brain volume • No evidence of myopathies or neuropathies. • Complexes I and IV (Western blot), ↓	c.1128_1129insT p.(Lys377*)	*HIBCH*	HIBCH (3-hydroxyisobutyryl-CoA hydrolase) deficiency	Reuter et al., 2014 [63] Study 35
52	5 months / Female	• Infantile spasms with hypsarrhythmia in EEG and psychomotor deterioration • Seizures • Behavioral disturbances • Mental retardation	N/A	m.3946G > A p.Glu214Lys	MT-ND1	Lennox–Gastaut syndrome	Delmiro et al., 2013 [64] Study 36
53	3 months / Female	• Early onset hypertrophic cardiomyopathy • Bronchiolitis like illness	N/A	c.1232C > T p.(Thr411Ile)	*MTO1*	Mitochondrial disorders	Baruffini et al., 2013 [65] Study 37
54	5 months / Female	• Upper respiratory illness • Hypertrophic cardiomyopathy • Wolf-Parkinson White syndrome • Psychomotor delay	N/A	c.1232C > T p.(Thr411Ile)	*MTO1*	Mitochondrial disorders	

Legend
- *Type of changes: arrow up* (↑) *– increased, arrow down* (↓) *– decreased, N – normal, N/A – not available*

Table 2
Summary of the quality and risk of bias assessment.

JBI Questions	STUDY																																		
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37
I	U	Y	U	U	Y	Y	U	Y	Y	Y	U	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	U	Y	U	Y	Y	Y	U	U	Y	Y	U	U	Y
II	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	U	U	Y	U	Y	Y	Y	Y	U	Y
III	Y	Y	Y	Y	U	Y	Y	U	U	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
IV	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
V	Y	Y	Y	Y	Y	Y	Y	X	Y	Y	U	Y	N	X	X	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y
VI	Y	Y	Y	Y	Y	Y	Y	X	U	Y	U	Y	N	X	X	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	Y	Y	Y	Y	Y
VII	Y	Y	Y	Y	U	Y	Y	X	Y	Y	U	X	N	X	X	Y	Y	Y	Y	N	Y	Y	Y	N	N	N	N	Y	N	N	Y	N	Y	N	N	Y	Y
VIII	Y	Y	Y	Y	Y	Y	Y	X	Y	Y	X	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	U	Y	Y
Total yes (Max 8)	6	8	7	7	6	8	7	3	6	7	3	6	5	4	4	7	7	8	4	7	8	8	8	4	6	7	3	7	4	5	6	7	7	7	6	6	8

The quality of each of the 37 studies was evaluated using the JBI critical appraisal checklist for case report. Results were listed in the table as yes (Y), no (X), unclear (U), and not applicable (N). The questions checklist is as follows:

I) Were patient's demographic characteristics clearly described?
II) Was the patient's history clearly described and presented as a timeline?
III) Was the current clinical condition of the patient on presentation clearly described?
IV) Were diagnostic tests or assessment methods and the results clearly described?
V) Was the intervention(s) or treatment procedure(s) clearly described?
VI) Was the post-intervention clinical condition clearly described?
VII) Were adverse events (harms) or unanticipated events identified and described?
VIII) Does the case report provide takeaway lessons?

biochemical screening tests contributed to only 21.3% of accurate diagnoses, highlighting their limited standalone diagnostic utility. This emphasizes the importance of utilizing biochemical tests in conjunction with other diagnostic approaches to ensure comprehensive and reliable diagnoses in clinical settings.

The field of IEM is constantly growing with new disorders and mechanisms being identified and characterized. Utilization of WES not only aids clinicians in the diagnosis of the disorder but also enables the identification of novel genes. This method allows clinicians to evaluate thousands of genes simultaneously, as compared to targeted sequencing, by utilizing next-generation sequencing technology. Subsequently, bioinformatic analyses will help to identify possible pathogenic variants from the thousands of genetic variants found in typical WES [67].

4.3. Association with cellular processes

Based on this review, 33 mutated genes corresponding to energy deficiency IEM in total were found to be associated with either metabolism or mitochondrial function, with a few genes were reported by multiple studies (*HADHB*, *ACO2*, and *HIBCH*) (Table 3). Mitochondrial metabolism is one of the key energy-producing systems that occurs throughout normal cellular development which also determines the cell fate [68]. This review revealed that the metabolic pathways involved were mostly in cellular bioenergetics in which their dysfunctions and deregulations leads to energy deficiency. For example, the mutated *HADHB* gene causes mitochondrial trifunctional protein deficiencies. This gene is part of a multi-enzyme complex crucial to the β-oxidation pathway. This mutant variant produces enzymes that are thermosensitive and hence reduces the enzymatic activity during increased body temperature such as fever. This disruption increases the likelihood of clinical decompensation, wherein the body's metabolic balance is compromised [34].

In the mitochondrion, an energy producing organelle, relations between energy deficiency to a putative mutational gene is not unexpected. Energy deficiency tends to be more associated with genes located in the mitochondrial genome. As the powerhouse of all mammalian cells, mitochondrial dysfunction causes a wide range of pathological illnesses. These resulting disorders are known to be due to altered function of the mitochondria's primary responsibility which is to produce energy in the form of adenosine triphosphate (ATP) by metabolizing organic substances.

Research also has proven that mitochondria are important in cellular metabolism and molecular interactions, including intracellular signalling. Shao et al. (2021) had identified a multiple ultra-rare genetic syndrome in patients with *GNB5S* and *GNB5L* mutations. Both genes were documented to be involved in the intracellular signalling pathway with the *GNB5* gene encoding proteins that were abundantly expressed in the central nervous system (Gβ5S) and one that was only expressed in the photoreceptor outer segments of the retina (Gβ5L). The *GNB5* mutation was reported to cause intellectual developmental disorder and a retinal signalling defect, such as bradyopsia, among other manifestations [38].

4.4. Mutational detection

In addition, this review reported that WES was able to identify mutations in 53 out of 54 cases across all 37 case reports, thereby making it a highly robust method for diagnosing energy-deficient IEM. The relevance of WES in diagnosing individuals with rare diseases like IEM, especially those who have a wide spectrum of energy deficient symptoms, was invaluable. The best aspect was that WES aids in mutation discovery more effectively than the standard sequencing approach, in which selected genes were sequenced based on the clinical symptoms. However, it was evident from our review that WES primarily detected nuclear gene alterations in the reported cases. Presumably this is because mitochondrial DNA (mtDNA) analysis is not a common practise

Table 3
Gene cellular processes associated to the IEM in each case reports.

Gene	Cellular process	Metabolism / organelle	Study number	Reference
GLS	Glutamine catabolism pathway	Metabolic pathway	1	[13]
PPCDC	Fatty acid pathway & TCA cycle		3	[15]
ACADM	Fatty acid pathway		4	[16]
HADHB	Beta oxidation		6 & 11	[18,23]
PHKA2	Glycogen breakdown		8	[20]
MOCS2	Molybdenum cofactor synthesis pathway		12	[24]
HMGCS2	Ketogenesis metabolic pathway		13	[25]
ACO2	TCA cycle		14, 24 & 29	[26,36,41]
SLC6A8	Creatine synthesis pathway (Creatine transport)		21	[33]
GAMT	Creatine synthesis pathway (Creatine transport)		21	[33]
ECSH1	Beta oxidation		23	[35]
CPS1	Urea cycle pathway		25	[37]
ECHS1	Beta oxidation		26	[38]
PCK1	Gluconeogenesis		28	[40]
HIBCH	Valine catabolism pathway		31 & 35	[43,47]
ITPA	Purine metabolism		34	[46]
GYS2	Glycogen synthesis pathway		33	[45]
GNB5L & GNB5S	Guanine nucleotide binding proteins machinery	Signalling pathway	10	[22]
DNAJC19	Mitochondrial transport machinery	Mitochondria	2	[14]
SQOR	Inner mitochondrial signalling protein		5	[17]
EARS2	Mito translation machinery		7	[19]
NDUFAF5	Mitochondrial respiratory chain		9	[21]
MTFMT	Mitochondrial translation		15	[27]
MICU1	Mitochondrial calcium channel complex		16	[28]
TUFM	Mito translation		18	[30]
LONP1	Encodes mitochondrial matrix protein		19	[31]
SSBP1	Mitochondrial biogenesis (Housekeeping gene)		20	[32]
TTC19	Complex III (MRC)		22	[34]
LIPT1	MRC cofactor		27	[39]
ACAD9	Complex I (MRC)		32	[44]
MT-ND1	Encode NADH dehydrogenase		36	[48]
MTO1	Encode mitochondria		37	[49]

in bioinformatic workflows for clinical WES [69]. Consequently, this may limit the variation coverage of mitochondrial genes that are involved in energy deficient IEM. However, this is understandable as nuclear DNA makes up most of human genome of 3.055 billion DNA base pairs compared to the mitochondrial genome of 16,569 DNA base pairs [70].

In situations when WES is unable to make a diagnosis, other genetic testing, such as copy number variant, non-coding variation, methylation testing, mtDNA sequencing, as well as whole genome sequencing, are among those that can be taken into consideration [71]. It is also important to acknowledge that every diagnostic test comes with its own set of inherent limitations. However, particularly in rare disorders such as IEM, they need to be addressed deliberately as they are an essential part in treatment decision making. The proposed strategies hold significant potential for bridging diagnostic gaps, particularly when precision medicine is being considered. Additionally, in certain instances, gaining insight into the molecular mechanism through functional studies can complement and validate the cause-and-effect relationship of the gene of interest.

5. Conclusion

In conclusion, the diagnostic approach plays a crucial role in addressing energy-deficient IEM, given the rarity and diverse array of symptoms that clinicians must navigate. As such, a definitive diagnosis significantly benefits patient therapy and care, especially in cases where precision medicine proves to be the most effective course of action. The WES approach offers a higher likelihood of improvement with its precise results, when compared to the standard practice of treating patients. It is strongly recommended that, in the near future, the bioinformatics workflow for clinical WES is to be complemented by mtDNA analysis, particularly for energy-deficient IEM.

CRediT authorship contribution statement

Fatimah Diana Amin Nordin: Writing – original draft, Validation, Formal analysis, Data curation, Conceptualization. **Affandi Omar:** Validation, Investigation, Formal analysis, Data curation. **Balqis Kamarudin:** Validation, Investigation, Formal analysis, Data curation. **Timothy Simpson:** Writing – review & editing, Validation, Supervision. **Julaina Abdul Jalil:** Validation, Supervision. **Yuh Fen Pung:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the first author.

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Appendix A. Supplementary data

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