REVIEW

Metabolic pathways and genes involved in treatable and non-treatable metabolic epilepsies. A comprehensive review and metabolic pathway analysis

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Abstract

More than 600 different metabolic disorders can lead to a clinical picture, where seizures are a main neurological manifestation, either as the primary clinical finding or as a part of a more complex phenotype. For these metabolic disorders, the term "metabolic epilepsy" is commonly used. About one in six metabolic epilepsies is treatable, constituting a well-defined subset of metabolic disorders, which is amenable to treatment targeting the primary cause of the seizures and reducing or preventing associated complications. However, the majority of metabolic disorders currently lack effective treatment, making them a major challenge both in clinical practice and in research. Herein, we provide an overview of both treatable and non-treatable metabolic epilepsies and discuss our current understanding of these disorders. We also perform pathway analysis in order to compare the pathways in which the genes associated with treatable and non-treatable metabolic epilepsies take part. This approach may orientate the research to particular pathways and explore novel treatment algorithms.

Keywords Metabolic epilepsy · Inborn errors of metabolism · Neurometabolic · Seizures · Treatment · Pathway analysis

Introduction

Epilepsy is a common neurological condition characterized by the occurrence of at least two non-provoked epileptic seizures appearing more than 24-hour apart (Berg et al. 2010). Therefore, seizures are the primary symptom of epilepsy. While epileptic seizures may appear in every brain, when the excitability of a specific brain region exceeds a defined threshold, epilepsy is distinguished by a lowered intrinsic seizure threshold, leading to an increased likelihood of recurrent spontaneous seizures (Balestrini et al. 2021).

According to the International League Against Epilepsy (ILAE), the causes of epilepsy can be classified into six groups: structural, genetic, infectious, metabolic, immune, and unknown (Scheffer et al. 2017).

Metabolic epilepsies are caused by a specific underlying metabolic abnormalities, leading to a higher risk of developing epilepsy (Almannai et al. 2021). Although pathogenesis of epilepsy is typically multifaceted, metabolic causes can be broadly classified into two major types: acquired and inherited. Acquired metabolic epilepsies may occur from factors such as nutritional deficiencies, autoimmune related metabolic disorders (e.g. celiac disease, type I diabetes mellitus, autoimmune cerebral folate deficiency), organ failure affecting substrate metabolism, or exposure to noxious agents such as drugs and toxins (Lin Lin Lee et al. 2018; Balestrini et al. 2021). It is noted that, although autoimmune disorders can also lead to seizures directly, autoimmune epilepsies fall outside the scope of this review. Inherited metabolic epilepsies arise from inborn errors of metabolism (IEMs), representing a less common cause of epilepsy. IEMs are congenital metabolic disorders (MDs)

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which result from genetic defects that disrupt essential biochemical pathways crucial for cellular function (Sharma and Prasad 2017). Although they can appear in any age, they are most prevalent in early childhood. Currently, about 600 metabolic epilepsies associated with IEMs have been identified, accounting for 42% of all monogenic diseases linked to epilepsy or seizures (Tumienė et al. 2018; Tumiene et al. 2022).

A significant portion of these MDs poses a tremendous challenge because they are often resistant to widely used antiepileptic medications. However, several metabolic epilepsies respond well to specific treatments. Treatable metabolic epilepsies can be managed by addressing the underlying cause of the seizure and by taking steps to prevent or minimize their complications (Bashiri et al. 2021).

Approaching metabolic epilepsies from a clinical perspective

Epileptic seizures are typically not the only symptoms in MDs. Therefore, MDs are less likely to clinically appear only with epileptic seizures without any other neurological, or metabolic features (Wolf et al. 2009). However, various types of seizures can occur in metabolic epilepsies. Consequently, these conditions require special attention when dealing with seizures that are refractory and/or long-lasting, of unknown origin in neonates or infants, intensified by fasting or high-protein meals, or exacerbated by antiepileptic drugs (AEDs). Furthermore, metabolic epilepsies should also be particularly considered in neonatal myoclonic encephalopathy and progressive myoclonic epilepsy phenotype in adolescence or early adulthood (Stockler et al. 2011; van Karnebeek et al. 2014).

Table 1 Features leading to the possible diagnosis of metabolic epilepsy

Features
Abnormal head size (microcephaly or macrocephaly
Aversion or intolerance to food
Developmental delay
Developmental regression
Dysmorphic facial features
Fluctuating course of illness
High-anion gap metabolic acidosis and metabolic derangement
Hypotonia
Ketonuria
Lens or retinal abnormalities
Movement disorders
Organomegaly
Parental consanguinity
Severe epilepsy in sibling
Signs of encephalopathy
Unusual body fluid odor

Table 1 displays additional features that may aid in diagnosing metabolic epilepsies.

A thorough examination, including laboratory tests and electroencephalogram (EEG), is essential when there is suspicion of metabolic epilepsy, along with brain imaging (Table 2). The initial laboratory assessment should encompass hyperammonemia, blood gas analysis to investigate potential metabolic acidosis, and/or hyperlactatemia (Stockler et al. 2011; Almannai et al. 2021). For cases where the diagnosis remains unclear, a second tier of biochemical tests, such as plasma amino acids profiles and acylcarnitine profiles, should be conducted based on clinical suspicion. Additional metabolic testing in urine, including S-sulphocysteine, purines and pyrimidines, guanidinoacetate, along with cerebrospinal fluid (CSF) analysis for glucose, amino acids, and folate, can provide further insights (Almannai et al. 2021). In summary, more comprehensive assessments may be contemplated, including global metabolomic profiling, genotyping to identify potential pathogenic variants, and whole exome and/or genome sequencing (Almannai and El-Hattab 2018). Notably, recent advancements suggest that whole exome sequencing (WES) can be more efficient than classical laboratory testing methods for early diagnosis of metabolic epilepsies (Mergnac et al. 2022).

Treatable metabolic epilepsies

The term "treatable metabolic epilepsy" refers to IEMs that can lead to epileptic seizures but when treated appropriately, can lead to a regression of the symptoms. These disorders can be classified in various ways characterized by biochemical pathway or organelle, as well as the age of onset (neonatal period and early infancy, late infancy and childhood, adolescent and adulthood, variable age at onset) (Sharma and Prasad 2017; Wirrell et al. 2022).

Online Resource 1 shows the treatable MDs that can lead to epilepsy, according to the International Classification of Inherited Metabolic Disorders (ICIMD), as well as the corresponding genes. Among these disorders, some of the most common ones have been chosen and are described below (Fig. 1).

Pyridoxine-dependent epilepsy

Pyridoxine-dependent epilepsy (PDE) (OMIM # 266100), also known as alpha-aminoadipic semialdehyde dehydrogenase deficiency, is an autosomal recessive (AR) epileptic encephalopathy caused by pathogenic variants in the antiquitin (ALDH7A1) gene (chromosome 5q23.2). It affects approximately one in 20,000 to 783,000 individuals and is resistant to conventional antiepileptic treatments.

Table 2 Laboratory, EEG, and imaging workup in possible metabolic epilepsy

Initial laboratory tests
 Ammonia
 Blood gases
 Routine CSF analysis
 Electrolytes
 Glucose
 Lactate
Additional biochemical tests in plasma
 α-aminoadipic semialdehyde
 Amino acids
 Ammonia
 Aylcarnitine profile
 Homocysteine
 Guanidinoacetate
 S-sulfocysteine
CSF laboratory tests
 5-methyltetrahydrofolate
 α-aminoadipic semialdehyde
 Amino acids
 Folate
 Glucose
 Pyridoxal phosphate
Routine Urine laboratory tests and Urine metabolic profiling
 α-aminoadipic semialdehyde
 Guanidinoacetate
 Homocysteine
 Organic acids
 Purine and pyrimidines
 S-sulfocysteine
Genotyping
 Allele specific polymerase chain reaction (PCR) (ARMS)
 Allele specific probes
 Denaturing gradient gel electrophoresis (DGGE)
 PCR amplification coupled with restriction enzyme analysis
 PCR product sequencing
 Single-strand conformation polymorphism (SSCP)
Whole sequencing
 Exome
 Genome
EEG findings
 Brust suppression
 Comb-like rhythm
 Generalized slowing
 Spike-wave, polyspike-wave complexes
 Status epilepticus in sleep
Neuroimaging findings
 Brain atrophy
 Cerebellar dysplasia
 Hemispheric hypoplasia
 Hypomyelination
 Hypoplasia or agenesis of the corpus collosum
 Leukodystrophy
 Focal cortical dysplasia
 Normal

Fig. 1 Treatable metabolic epilepsies that described below (created with BioRender.com: https://www.biorender.com/)

This condition arises from a deficiency in the enzyme α-aminoadipic semialdehyde dehydrogenase (antiquitin). ALDH7A1 is pivotal in lysine catabolism, functioning as a Δ1-piperideine-6-carboxylate (P6C) and alpha-aminoadipic semialdehyde (α-AASA) dehydrogenase (Stockler et al. 2011). The deficiency of this enzyme leads to the accumulation of α-AASA and P6C, which can inactivate pyridoxal-5-phosphate (PLP), an essential cofactor in neurotransmitter metabolism. The accumulation of α-AASA may also contribute to the pathogenesis of PDE, as its reactive nature as a semialdehyde can undergo various chemical reactions and interact with multiple metabolic pathways (Stockler et al. 2011).

Presentation

PDE typically emerges within the first hours or days of life, with approximately 70% of cases experiencing neonatal seizures shortly after birth, although there are atypical cases with later onset (Coughlin et al. 2019; Osman et al. 2020). In some instances, seizures may even occur in utero, commencing in the late third trimester and presenting as excessive and jerky fetal movements. The suspicion of PDE arises in cases involving recurrent, often myoclonic,

seizures, without apparent gestational or perinatal issues and exhibiting poor responsiveness to pharmaceutical treatment (Dulac et al. 2014). In classical PDE cases seizures may be accompanied by various clinical features, including abnormal fetal movements, symptoms resembling birth asphyxia or hypoxic-ischemic encephalopathy (HIE), irritability, abnormal cry, vomiting, abdominal distention, dystonic movements, startle response, paroxysmal facial grimacing, abnormal eye movements, respiratory distress, hepatomegaly, acidosis, shock, and hypothermia (Van Karnebeek and Jaggumantri 2015). PDE patients commonly face neurodevelopmental disabilities, such as developmental delay and intellectual disability, particularly affecting expressive language domain, coupled with a low-normal motor and performance IQ scores (Schmitt et al. 2010).

Diagnosis

Biochemical tests reveal elevated levels of α-AASA (specific) and pipecolic acid (non-specific) in plasma, urine, and CSF, persisting even under treatment, rendering them valuable diagnostic indicators (Lin Lin Lee et al. 2018). The elevated α-AASA levels are often several times over the upper normal limit, influenced by factors such as the specific pathogenic variant, the age of the patient, pyridoxine (PN) treatment, and potential lysine intake (Stockler et al. 2011). However, as the determination of α-AASA is restricted to a few laboratories globally, pipecolic acid can be used as an initial screening test. In instances where pipecolic acid results are inconclusive or negative despite strong clinical suspicion, further α-AASA analysis can be pursued (Stockler et al. 2011). The diagnosis is further supported by identifying pathogenic variants in the ALDH7A1 gene.

Treatment

Initiating PN therapy should not be postponed for diagnostic purposes. In classical PDE, seizures occurring within the first month postpartum can usually be suppressed in less than an hour with intravenous PN administration, and changing to oral PN for long-term management. However, seizures may restart within days if PN is discontinued, and their immediate resolution is observed upon treatment reinitiation (Van Karnebeek and Jaggumantri 2015). In late-onset PDE, it may take more than seven days of PN administration before a seizure regression is observed. Maintaining a daily dose below 500 mg is crucial due to the association of PN treatment with sensory peripheral neuropathy. If neuropathy is evident, the PN dose should be minimized to the most effective level (Rahman et al. 2013; Dulac et al. 2014). In cases with an unclear response to PN, folinic acid treatment may

be considered beneficial, although the exact mechanism remains unclear. Folinic acid-responsive epilepsy shares biochemical markers with pyridoxine-dependent epilepsy. However, high doses of folinic acid may exacerbate seizures, necessitating careful monitoring of clinical benefits (Stockler et al. 2011; van Karnebeek et al. 2016; Kava et al. 2020). Additionally, the treatment plan often involves dietary lysine restriction (Kava et al. 2020). Notably, infants with PDE pose a recurrent risk of up to 25% for PDE in subsequent pregnancies, and pregnant women carrying a fetus at risk should receive supplemental PN (Stockler et al. 2011).

Pyridoxal phosphate-responsive epilepsy

Pyridoxal phosphate-responsive epilepsy (OMIM # 610090), also known as pyridoxamine 5'-phosphate oxidase (PNPO) deficiency, is a very rare AR neonatal epileptic encephalopathy, occurring at a rate of one to nine in 1,000,000 births. This disorder is attributed to pathogenic variants in the PNPO gene (chromosome 17q21.32), resulting in a deficiency of the PNPO enzyme. PNPO plays a crucial role in catalyzing the oxidation of pyridoxine 5'-phosphate (PNP) and pyridoxamine 5'-phosphate (PMP) into PLP, the active form of PN (Mills et al. 2014). PLP, as a vital vitamin B6 cofactor, participates in various pathways and neuronal processes, including amino acids and neurotransmitter metabolism, particularly gamma-aminobutyric acid (GABA) biosynthesis (Mills et al. 2014).

Presentation

This deficiency usually manifests in the first few days of life, with over 80% of cases appearing within the first week. Common symptoms include lethargy, hypotonia, and a severe seizure disorder that is unresponsive to conventional anticonvulsant medications and can be life-threatening if not treated (Mills et al. 2005; Poretti et al. 2013). Infants affected by PLP-dependent epilepsy are often born prematurely, and some may exhibit intrauterine seizures characterized by abnormal fetal movements in the third trimester, as noticed by the mother. Various seizure types have been observed in these patients, such as focal, generalized tonic or myoclonic seizures, infantile spasms, atonic or generalized clonic seizures, and status epilepticus (Di Salvo et al. 2017). Additionally, a constellation of systemic and neurological symptoms may be present, including movement disorders, pigmentary retinopathy, irritability, abnormal eye movements, developmental delay, and intellectual disability (Alghamdi et al. 2021).

Diagnosis

EEG examinations may reveal electrical status epilepticus during sleep (Veerapandiyan et al. 2011). Diagnosis is supported by demonstrating seizure cessation and corresponding EEG changes with PLP administration, typically within an hour, although some affected infants may respond to parenteral nutrition (Mills et al. 2014). The clinical diagnosis is further supported by reduced PLP levels in CSF. Further evidence indicating reduced activity of enzymes using PLP as a cofactor include elevated glycine and threonine plasma and CSF levels, an increase of 3-methoxytyrosine, and a reduction of 5-hydroxyindoleacetic acid and homovanillic acid in CSF (Almannai et al. 2021). Genotyping of the PNPO gene can confirm the diagnosis.

Treatment

Traditional AEDs can be proven ineffective against seizures, however they can generally be suppressed through continuous supplementation of PLP (Hoffmann et al. 2007). It is advisable to monitor liver function in children undergoing PLP treatment, particularly when administering high doses, as there have been reported cases of abnormal liver function. Temporary dose reduction may be necessary if mild gastrointestinal disturbance and liver enzyme elevation are observed (Alghamdi et al. 2021).

Early-onset vitamin B6-dependent epilepsy

Early-onset vitamin B6-dependent epilepsy (EPVB6D) (OMIM # 617290), also known as PLPBP deficiency, is a very rare disorder (< 50 cases have been reported worldwide) caused by biallelic pathogenic variants in the PLPBP gene (previously called PROSC) (chromosome 8p11.23) (Darin et al. 2016; Plecko et al. 2017; Heath et al. 2021). This gene encodes an evolutionarily conserved PLP-binding protein which is crucial in vitamin B6 homeostasis, by providing PLP to apoenzymes, thus minimizing the toxicity associated with excess unbound PLP (Tremiño et al. 2017; Johnstone et al. 2019). Pathogenic variants in the PLPBP gene lead to dysfunction of several PLP-dependent enzymes, such as glycine cleavage enzyme (GCV) and aromatic l-amino acid decarboxylase (Shiraku et al. 2018; Johnstone et al. 2019).

Presentation

The most distinctive symptom of EPVB6D is neonatal seizures; however, the initial seizure may manifest beyond the neonatal period, often during childhood. Myoclonic and generalized tonic-clonic seizures are the most frequently observed types of seizures. Seizures tend to be resistant or only partially responsive to anti-seizure medications, yet they typically exhibit an immediate positive response to vitamin B6 administered as PN and/or PLP. More than 50% of patients with PLPBP deficiency experience various degrees of neurodevelopmental issues, such as intellectual disability and developmental abnormalities (Shiraku et al. 2018).

Diagnosis

In contrast to other causes of B6-dependent epilepsies, this disorder lacks specific biochemical markers (Plecko et al. 2017). Common observations typically involve increased lactate with associated metabolic acidosis and high glycine levels, while the most common finding in urine is elevated vanillactic acid level (Heath et al. 2021). The molecular diagnosis involves the identification of pathogenic variants in PLPBP gene (Shiraku et al. 2018; Heath et al. 2021).

Treatment

Early administration of PN and/or PLP, which should be maintained throughout the patient's life, is crucial (Darin et al. 2016). Additionally, a significant number of cases necessitate the use of adjunct anti-seizure medications to attain optimal control of seizures.

Biotinidase deficiency

Biotinidase deficiency (BD) (OMIM # 253260) is a rare (one in 60,000 births) AR MD attributed to pathogenic variants in the BTD gene (chromosome 3p25.1), responsible for encoding the biotinidase enzyme (Gowda et al. 2023). This enzyme plays a crucial role in cleaving biotin, an essential cofactor for various carboxylase enzymes, from biocytin and biotinyl-peptides, facilitating the recycling of biotin (Wolf et al. 1985). Patients with BD are unable to effectively recycle biotin, leading to deficiency in multiple carboxylase enzymes and the accumulation of potentially neurotoxic and epileptogenic metabolites (Mastrangelo 2018).

Presentation

The time of onset of BD varies from two weeks to two years, based on the level of the enzyme activity. On average, symptoms may manifest as early as 3.5 months, but some patients may experience symptoms much later in life (Canda et al. 2020). Patients, depending on the degree of the enzyme activity, categorized into two groups: patients with profound deficiency (< 10% of enzyme activity) and others with partial deficiency (10–30% of enzyme activity) (Wolf 2010). Partial cases may exhibit minimal or no symptoms,

while in cases of profound deficiency, rapid initiation of treatment is crucial, as it can lead to coma or death if left untreated (Canda et al. 2020).

The clinical manifestations of BD are diverse, but in most untreated cases, patients may exhibit seizures, hypotonia, developmental delay, vision and hearing problems, breathing, and feeding difficulties (Akgun et al. 2021). Feeding difficulties may involve vomiting and gagging, while breathing problems may manifest as stridor, apnea, and hyperventilation. Additionally, the disorder is characterized by alopecia and skin rash. Patients may also exhibit neuromuscular symptoms such as muscular atrophy, paresis, and prominent peripheral muscle denervation (Tankeu et al. 2023).

Diagnosis

Biochemical disturbances associated with BD encompass lactic acidemia, hyperammonemia, and/or metabolic acidosis (Almannai et al. 2021). Metabolic abnormalities include elevated levels of abnormal organic acid metabolites such as 3-methylcrotonylglycine, 3-hydroxyisovalerate, methylcitrate, propionylglycine, and hydroxypropionate (Canda et al. 2020). Diagnosis of BD can be confirmed by assessing biotinidase enzyme activity, although in some cases carriers may exhibit serum biotinidase activity similar to patients with partial BD (Canda et al. 2020). In any case, the disease can be diagnosed by identifying pathogenic variants in the BTD gene, with all types of variants being found in patients (Canda et al. 2020). Neuroimaging typically reveals cerebral atrophy and patchy signal in cerebral white matter (Gowda et al. 2023).

Treatment

BD typically shows a favorable respond to oral biotin supplementation (Canda et al. 2020). However, improvements in seizures and movement disorders may require a few hours to days, while skin manifestations may need several weeks to resolve. If standard dose of biotin is insufficient and clinical signs persist, an increased dosage is recommended.

Holocarboxylase synthetase deficiency

Holocarboxylase synthetase deficiency (HLCSD) (OMIM # 253270) is a rare AR disorder of biotin metabolism. It is caused bypathogenic variants in the holocarboxylase synthetase (HLCS) gene (chromosome 21q22.13) and resulting in multiple carboxylase deficiency (Ling et al. 2023). The global incidence of HLCS deficiency has been reported at one in 200,000 births (Donti et al. 2016). HLCS is the enzyme that carries out the attachment of biotin to the carboxylase enzymes, subsequently activating them. A defect in HLCS leads to reduced activities of biotin-dependent carboxylases, resulting in imbalances in the metabolism of amino acids, fatty acids, and carbohydrates (Wu et al. 2020).

Presentation

BD and HLCSD share overlapping features. HLCSD typically presents early, often before three months of age, with various symptoms, such as seizures, hypotonia, lethargy, vomiting, hypothermia, tachypnea, alopecia, and skin rash (Bandaralage et al. 2016; Donti et al. 2016; Almannai et al. 2021). The types of seizures include generalized tonic-clonic and myoclonic seizures, as well as infantile spasms (Almannai et al. 2021). Prolonged complications might involve intellectual disability, microcephaly, ataxia, and movement disorders (Cadieux-Dion et al. 2021). Left untreated, could advance to a critical stage of metabolic acidosis, leading to either coma or death (Ling et al. 2023).

Diagnosis

Biochemical testing involves examining the plasma amino acid profile and conducting urine organic acid analysis (Cadieux-Dion et al. 2021). The molecular confirmation of HLCSD is possible by detecting pathogenic variants in the HLCS gene.

Treatment

HLCSD is treatable with high-dose oral biotin supplementation (Meguro et al. 2022).

Cerebral folate deficiency

Cerebral folate deficiency (CFD) (OMIM # 613068), also referred to folate receptor alpha deficiency, is a rare progressive neurological disorder occurring in less than one in 1,000,000 births. It follows an AR inheritance pattern and results from anomalies in the folate receptor alpha (FOLR1) gene (chromosome 11q13.4), responsible for coding the FOLR1 protein (Almannai et al. 2021). The primary form of folate transport is 5-methyltetrahydrofolate (5-MTHF), prevalent in both plasma and CSF. The folate receptor alpha (FRα) plays a vital role as a major transporter of folate across the blood-brain barrier. Impairments in this transporter lead to low levels of 5-MTHF in the CSF. 5-MTHF, serving as the active folate metabolite, is crucial for myelin formation and neurotransmitter synthesis. It actively participates in the synthesis of DNA, amino acids, proteins, and neurotransmitters, functioning as a methyl donor in homocysteine remethylation (Masingue et al. 2019). Folate deficiency results in disruptions to myelin metabolism and

neurodegeneration (Kanmaz et al. 2023). Secondary forms of CFD have been identified in cases involving chronic use of anti-folate medications and in diverse conditions like Aicardi-Goutieres and Rett syndrome (Ramaekers et al. 2003; Blau et al. 2003).

Presentation

The most common symptoms typically appear between four months and early childhood and encompass cerebellar ataxia, severe developmental regression, movement disorders, spastic paraplegia, irritability, progressive visual and hearing impairment, as well as sleep disturbance. Generalized tonic-clonic, tonic, atonic, and myoclonic seizures are also observed (Almannai and El-Hattab 2018).

Diagnosis

The diagnosis relies on detecting reduced levels of 5-MTHF in CSF while maintaining normal levels of plasma folate (Kanmaz et al. 2023). Molecular confirmation of the diagnosis involves identifying pathogenic variants in the FOLR1 gene (Al-Baradie and Chaudhary 2014; Kanmaz et al. 2023). Neuroimaging findings include cerebellar atrophy and hypomyelination or leukodystrophy (Kanmaz et al. 2023).

Treatment

Initiating early treatment through oral administration of folinic acid has shown efficacy in restoring folate levels in CSF and improving clinical symptoms (Steinfeld et al. 2009; Ferreira et al. 2016).

Glucose transporter 1 (GLUT1) deficiency

GLUT1 deficiency (OMIM # 606777) is a rare (one to two in 100,000 births) metabolic encephalopathy resulting from pathogenic variants in the solute carrier family 2 (facilitated glucose transporter), member 1 (SLC2A1) gene (chromosome 1p34.2), responsible for encoding GLUT1 (Castellotti et al. 2019; López-Rivera et al. 2020). In most instances, these pathogenic variants occur de novo, while in familial cases, it follows an autosomal dominant (AD) pattern and, rarely, an AR pattern (Hao et al. 2017). The disorder is characterized by a deficiency of GLUT1, a crucial transporter facilitating glucose passage through the blood-brain barrier as well as other tissue barriers (Koch and Weber 2019). As glucose serves as the primary energy source for the brain, disruptions in this transporter result in impaired energy supply to the brain (Olivotto et al. 2022).

Presentation

Based on phenotype, patients can be categorized into four groups: minimal, mild, moderate, and severe (Olivotto et al. 2022). Patients with missense pathogenic variants typically exhibit symptoms ranging from moderate to mild. However, establishing clear correlations between the phenotype and genotype is challenging, as patients with identical pathogenic variants often display diverse clinical manifestations. This implies the presence of additional factors, like disease-modifying genes and proteins, which may influence the phenotype and potentially play a role in condition's complex pathophysiology.

GLUT1 deficiency is typically characterized from refractory seizures, developmental delay, microcephaly, and a complex movement disorder characterized by dystonia and ataxia (Winczewska-Wiktor et al. 2020; Hu et al. 2021). Epilepsy is the most common manifestation, often initiating before second year of life and frequently within the first months, being resistant to conventional AEDs (De Giorgis et al. 2015). Seizures may manifest in various types, with myoclonic-atonic seizures being quite common. However, additional clinical manifestations may emerge over time, including alternating hemiplegia, paroxysmal exertion-induced dystonia, choreoathetosis, and other intermittent events including migraine (Wang et al. 1993).

Diagnosis

Consideration of GLUT1 deficiency is crucial in the differential diagnosis of drug resistand epilepsy. A significant diagnostic sign is the presence of paroxysmal exercise-induced dyskinesia, which may worsen after periods of fasting. In general, all symptoms are susceptible to exacerbation during fasting. The diagnosis can be affirmed by the observation of hypoglycorrhachia and molecularly confirmed through mutation analysis of the SLC2A1 gene (Hu et al. 2021; Kolic et al. 2021). EEG findings during fasting often reveal slow activity with multifocal or generalized high-amplitude spikes. After a carbohydrate meal, EEG may indicate a reduction in epileptic discharges (Klepper et al. 2020). Mild cases frequently evade diagnosis (Olivotto et al. 2022).

Treatment

The treatment plan involves employing ketogenic diet, characterized by a high-fat and low-carbohydrate composition, which supplies ketone bodies as an alternative energy source to the brain (Almannai et al. 2021; Kolic et al. 2021). While the ketogenic diet may contribute to seizure control, its impact on overall development is less conspicuous.

Generally, the earlier the ketogenic diet is initiated, the more favorable the prognosis becomes (Kass et al. 2016).

Non-treatable metabolic epilepsies

As outlined above, certain metabolic epilepsies are treatable. However, the majority of these conditions currently lack effective therapeutic options. Online Resource 2 shows the untreatable MDs that can lead to epilepsy, according to the ICIMD, as well as the corresponding genes. Among these disorders, some of the most prevalent ones are outlined and discussed in the following section (Fig. 2).

Adenylosuccinate lyase deficiency

Adenylosuccinate lyase (ADSL) deficiency (OMIM # 103050) is a rare AR disorder affecting purine metabolism due to pathogenic variants in the ADSL gene (chromosome 22q13.1) (Mastrogiorgio et al. 2021). To date, over 120 cases have been reported, with an estimated frequency of approximately one in 1,250,000 births (Ferreira 2017; Dewulf et al. 2022). ADSL is an enzyme that catalyzes two non-sequential steps in the purine synthesis pathway. Firstly, it converts succinylaminoimadazole carboxamide ribotide (SAICAR) to aminoimidazole carboxamide ribotide (AICAR), and secondly, it converts adenylosuccinate into adenosine monophosphate (AMP). The disorder leads to the accumulation of SAICAR and succinyladenosine (S-Ado),

causing adverse effects on the nervous system (Wang et al. 2022).

Presentation

ADSL deficiency is characterized from a wide range of symptoms and, depending on the age of onset and clinical severity, can be categorized into three primary forms: type I (severe), type II (mild), and the fatal neonatal type (Mastrogiorgio et al. 2021). Type I, the most common form, is marked by early onset seizures, severe psychomotor retardation, and microcephaly (Sharma and Prasad 2017; Cutillo et al. 2024). Seizures typically emerge within the first few months of life, displaying variable semiology, including myoclonus, focal onset seizures with or without impaired awareness, epileptic spasms, and status epilepticus. Concurrently, autistic features are frequently observed (Sharma and Prasad 2017; Almannai et al. 2021; Cutillo et al. 2024). Prenatal manifestations may include microcephaly, fetal hypokinesia, impaired intrauterine growth, and a loss of fetal heart rate variability (Hegde et al. 2019). The mild form (type II) exhibits later onset, hypotonia, mild to moderate developmental delay, ataxia, and autistic features (Almannai et al. 2021; Mastrogiorgio et al. 2021). Seizures, if present, typically emerge between the second and fourth years of life. The fatal neonatal form can manifest in the neonatal period, representing the most severe type. It is characterized by hypotonia, encephalopathy, severe seizures, and early death. Affected infants may also display

Fig. 2 Non-treatable metabolic epilepsies that described below (created with BioRender.com: https://www.biorender.com/)

NON-TREATABLE METABOLIC EPILEPSIES

Adenylosuccinate lyase deficiency

GABA transaminase deficiency

Dihydropyrimidine dehydrogenase deficiency

Dihydropyrimidinase deficiency

Glucocerebrosidase deficiency

Sulfite oxidase deficiency

signs of intrauterine growth retardation and microcephaly (Mastrogiorgio et al. 2021; Cutillo et al. 2024).

Diagnosis

The diagnosis relies on identifying elevated levels of purine metabolites in urine and can be confirmed through enzymatic assessment of ADSL enzyme activity in liver, kidney, fibroblasts, or lymphocytes. Additionally, molecular genetic testing for pathogenic variants in the ADSL gene serves as a diagnostic tool (Sharma and Prasad 2017; Almannai et al. 2021). In most cases, patients are compound heterozygotes (Wang et al. 2022). Regarding disease severity, the S-Ado/SAICAR ratio in body fluids serves as a biomarker, where a lower ratio corresponds to more severe clinical symptoms in patients (Mastrogiorgio et al. 2021). Neuroimaging may reveal hypomyelination, brain atrophy, and cerebellar atrophy (Almannai et al. 2021).

GABA transaminase deficiency

GABA transaminase deficiency (OMIM # 613163) is a rare AR neurometabolic disorder with a prevalence of less than one in 1,000,000 births. This disorder arises from pathogenic variants in the ABAT gene (chromosome 16p13.2). GABA, the primary inhibitory neurotransmitter in the human nervous system, undergoes metabolism to succinic semialdehyde, thus reducing neurotransmitter levels and activity. The role of GABA transaminase is to convert GABA to succinic semialdehyde, facilitating the oxidative metabolism of GABA through the tricarboxylic acid cycle (Kennedy et al. 2019). GABA transaminase deficiency results in elevated endogenous GABA levels, leading to the symptomatic appearance of the disorder.

Presentation

As a neurometabolic disorder, the initial manifestations of GABA-transaminase deficiency commonly involve hypotonia and may be accompanied by drug resistant seizures, including infantile spasms. Additional symptoms include psychomotor retardation, hyperreflexia, and abnormalities in brain magnetic resonance imaging (MRI) and EEG (Kennedy et al. 2019).

Diagnosis

Conventional diagnostic approaches for GABA-transaminase deficiency involve conducting enzymatic test of ABAT, examining neurotransmitter profile in CSF, and performing molecular test on ABAT gene to identify pathogenic variants (Kennedy et al. 2019).

Dihydropyrimidine dehydrogenase deficiency

Dihydropyrimidine dehydrogenase (DPD) deficiency (OMIM #274270) is a rare AR disease associated with the DPYD gene (chromosome 1p21.3) (Kieran et al. 2024). The DPD enzyme is responsible for converting uracil to dihydrouracil and thymine to dihydrothymine. In cases of DPD deficiency, there is an accumulation of uracil and thymine, leading to decreased levels of the final products beta-alanine and beta-aminoisobutyrate. The reduced levels of beta-alanine, a neuromodulator with the ability to hinder GABA reuptake, may contribute to the manifestation of neurological symptoms (Almannai et al. 2021). Partial DPD deficiency is present in 3–5% of the general population, while complete deficiency is observed in 0.1% (Schmitt et al. 2023).

Presentation

DPD deficiency exhibits a highly diverse range of symptoms. Typically appearing in infancy, the disease may also manifest later. The majority of patients experience seizures and developmental delay, often accompanied by growth retardation, hyperreflexia, autistic features, hypertonia, microcephaly, and ocular abnormalities. Patients, as well as carriers, display heightened sensitivity to 5-fluorouracil, resulting in severe toxicity (Almannai et al. 2021).

Diagnosis

Biochemical testing shows increased levels of uracil and thymine in urine, plasma, and CSF. Enzymatic confirmation of the diagnosis involves measuring DPD enzyme activity in fibroblasts, liver, and blood mononuclear cells. Molecular confirmation is achieved through the identification of pathogenic variants in the DPYD gene. Neuroimaging commonly reveals cerebral atrophy and white matter abnormalities in most patients (Almannai et al. 2021; Schmitt et al. 2023).

Dihydropyrimidinase deficiency

Dihydropyrimidinase (DHP) deficiency (OMIM # 222748) is a rare AR disorder, with approximately 35 reported cases, caused by homozygous or compound heterozygous mutations in the DPYS gene (chromosome 8q22.3) (Albokhari et al. 2023). This gene encodes the DHP enzyme, responsible for breaking down pyrimidines (Mirzaei et al. 2020). It catalyzes the cleavage of dihydrouracil into beta-ureidopropionate and dihydrothymine into beta-ureidoisobutyrate. DHP deficiency leads to an accumulation of dihydrouracil and dihydrothymine while depleting the

final products beta-alanine and beta-aminoisobutyrate (Almannai et al. 2021).

Presentation

The clinical manifestations of DHP deficiency exhibit a wide spectrum, ranging from asymptomatic cases to severe affected individuals (Mirzaei et al. 2020; Albokhari et al. 2023). Symptomatic children may display epilepsy, developmental delay, growth retardation, hypotonia, microcephaly, and white matter abnormalities (Mirzaei et al. 2020). Gastrointestinal issues are present in nearly half of the cases. Both patients and carriers show heightened sensitivity to 5-fluorouracil, resulting in severe toxicity (Almannai et al. 2021).

Diagnosis

Patients present a substantial elevation in urinary dihydrouracil and dihydrothymine levels. The diagnosis can be confirmed by assessing the activity of the DHP enzyme through liver biopsy. Molecular confirmation of the diagnosis involves identifying pathogenic variants in the DPYS gene (Almannai et al. 2021).

Glucocerebrosidase deficiency (Gaucher disease)

Glucocerebrosidase deficiency (OMIM # 230800, 230900, 231000) is an AR lysosomal storage disorder, with a prevalence estimated between one in 40,000 to 60,000 live births (Stirnemann et al. 2017). It is caused by biallelic mutations in the GBA gene (chromosome 1q21) (Manisha and Phadke 2024). The GBA gene encodes the lysosomal enzyme glucocerebrosidase, and a deficiency in this enzyme leads to the accumulation of glucosylceramide (also known as beta-glucocerebrosidase) deposits in cells of the liver, spleen, lungs, and bone marrow, leading to the formation of Gaucher cells (Carvoeiro et al. 2024).

Presentation

Gaucher disease exhibits varied symptoms and is classified into three primary clinical types: type 1, which constitutes the majority of cases (90–95% of all cases) and is characterized by chronic and non-neurological symptoms such as anemia, hepatosplenomegaly, thrombocytopenia, lung and bone diseases; type 2, an acute neurological form with onset before the age of two, rapid psychomotor decline, and early mortality; and type 3, a subacute neurological form with slower progression and survival until the third or fourth decade of age, usually manifesting before the age of two

(Almannai et al. 2021; Carvoeiro et al. 2024; Manisha and Phadke 2024).

Diagnosis

The enzymatic diagnosis involves confirming decreased glucocerebrosidase enzyme activity, while the molecular diagnosis is confirmed through identifying pathogenic variants in the GBA gene (Almannai et al. 2021).

Sulfite oxidase deficiency

Sulfite oxidase deficiency (OMIM # 272300) is a very rare AR MD that typically manifests in the neonatal or early infantile period and is caused by loss-of-function pathogenic variants in the sulfite oxidase (SUOX) gene (chromosome 12q13.2) (Zhao et al. 2021). SUOX functions as a molybdo-hemoprotein and can be found in the intermembrane space of mitochondria. This enzyme is important in catalyzing the conversion of cytotoxic sulfites (SO_3^{2-}) into non-toxic sulfates (SO_4^{2-}) during the final stage of oxidizing sulfur-containing amino acids methionine and cysteine (Li et al. 2022).

Presentation

Cases with a neonatal onset of sulfite oxidase deficiency exhibit extremely severe clinical symptoms, often resulting in early infancy mortality (Zhang et al. 2022). Common clinical features include profound developmental delay, drug-resistant seizures, microcephaly, progressive encephalopathy, ectopia lentis, abnormal movements, and feeding difficulties (Mhanni et al. 2020). Conversely, patients with a later age of onset typically present with cerebral palsy, encephalomalacia, and severe developmental delay (Zhang et al. 2022).

Diagnosis

The most common biochemical features facilitating the diagnosis of sulfite oxidase deficiency include increased urinary excretion of sulfite, thiosulfate, and S-sulfocysteine, along with low total homocysteine and normal methionine levels in plasma. Additionally, reduced cystine levels and normal hypoxanthine, xanthine, and uric acid levels in both plasma and urine are observed (Mhanni et al. 2020; Zhao et al. 2021). Neuroimaging features often reveal ventriculomegaly, hypoplastic corpus callosum, cerebral and cerebellar atrophy, as well as cystic supratentorial white matter degeneration (Zhang et al. 2022). Molecular confirmation of the diagnosis involves identifying pathogenic variants in the SUOX gene.

Pathway analysis

Pathway analysis of disease-associated genes is a wide class of methods that aids in the substantial clarification of the developmental origins, the underlying pathophysiology, and the application of targeted treatment modalities (La Ferlita et al. 2022). We performed pathway analysis in order to understand the functional significance of genes associated with treatable and non-treatable metabolic epilepsies. This approach may help the genetic laboratory investigation to search particular pathways and explore novel therapeutic algorithms.

Analysis was conducted using the Reactome (version 88) pathway database (https://reactome.org/) (Gillespie et al. 2022). Reactome analysis is a type of overrepresentation analysis, namely a statistical test based on the hypergeometric distribution. Its purpose is to determine whether certain pathways are over-represented within the submitted data. This test produces a probability score, which is corrected for false discovery rate (FDR) using the Benjamani-Hochberg method. $P < 0.05$ and FDR < 0.05 were selected as the criteria for statistical significance. It is noted that pathways are standardized nomenclature used in the Reactome database. For the plotting, we used the R packages ggplot2 (v3.5.0) and VennDiagram (v1.6.0).

For the analysis we used two groups: (a) the genes that are associated with treatable metabolic epilepsies (Online Resource 1) ($n = 110$), and (b) the genes that are associated with non-treatable metabolic epilepsies (Online Resource 2) ($n = 499$). We identified the extended pathways in which they take part and crossmatched the generated data.

For group a), 57 pathways were considered as statistically significant (Fig. 3; Table 3). As presented in Fig. 3; Table 3, "Metabolism", "Metabolism of amino acids and derivatives" and "Metabolism of vitamins and cofactors" are the three pathways most strongly associated with treatable metabolic epilepsies, according to our results.

For group b), 59 of these pathways were considered statistically significant (Fig. 4). Those pathways with higher probability are presented in Table 4. The pathways that seem to be most closely associated with non-treatable metabolic epilepsies are the following: "Metabolism", "Metabolism of proteins", "Aerobic respiration and respiratory electron transport", "tRNA processing".

We compared the pathways of group a) and b) and we found that only 17 pathways are included in both groups (Fig. 5). Table 5 demonstrate those overlapping pathways.

Discussion

Metabolic epilepsies, a subset of epileptic disorders caused by metabolic abnormalities, can arise from inherited or acquired disruptions in cellular metabolism. To date, there are 2946 epilepsy-associated genes, 1506 of which are identified to be associated with epilepsy based on the OMIM
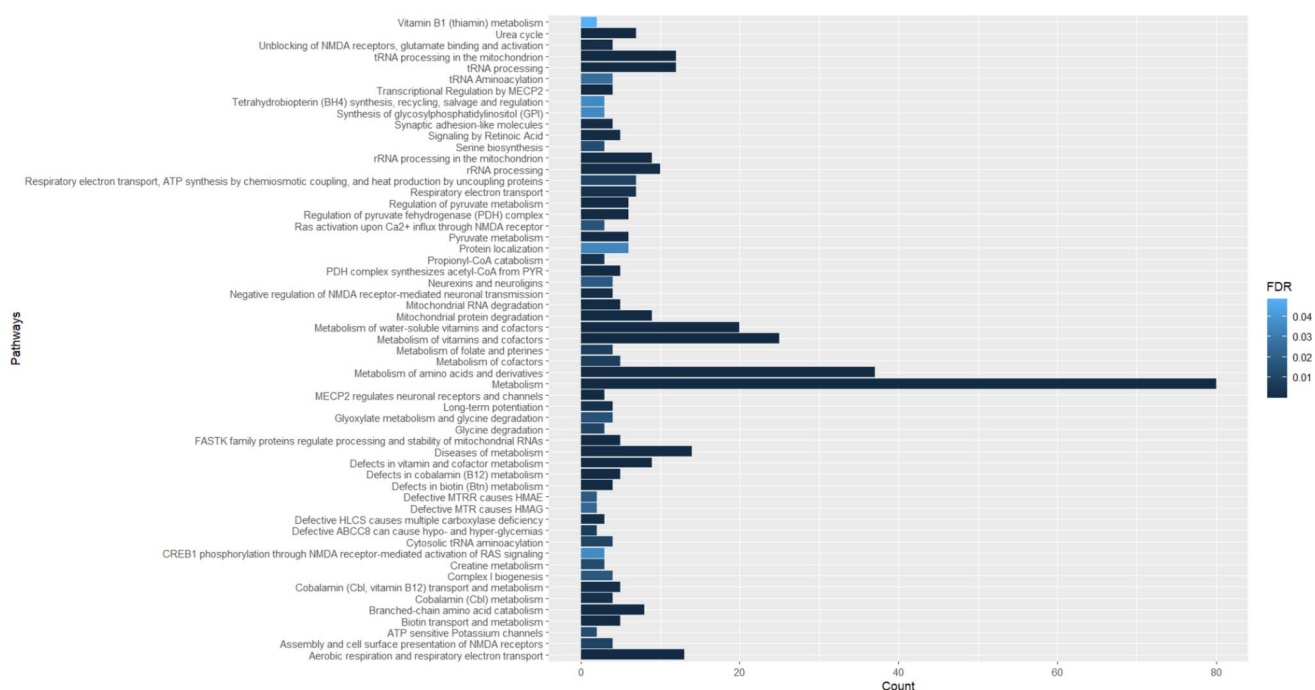

Fig. 3 Pathway analysis of genes associated with treatable metabolic epilepsies. y-Axis indicates the pathway name, x-axis indicates the number of genes of interest that t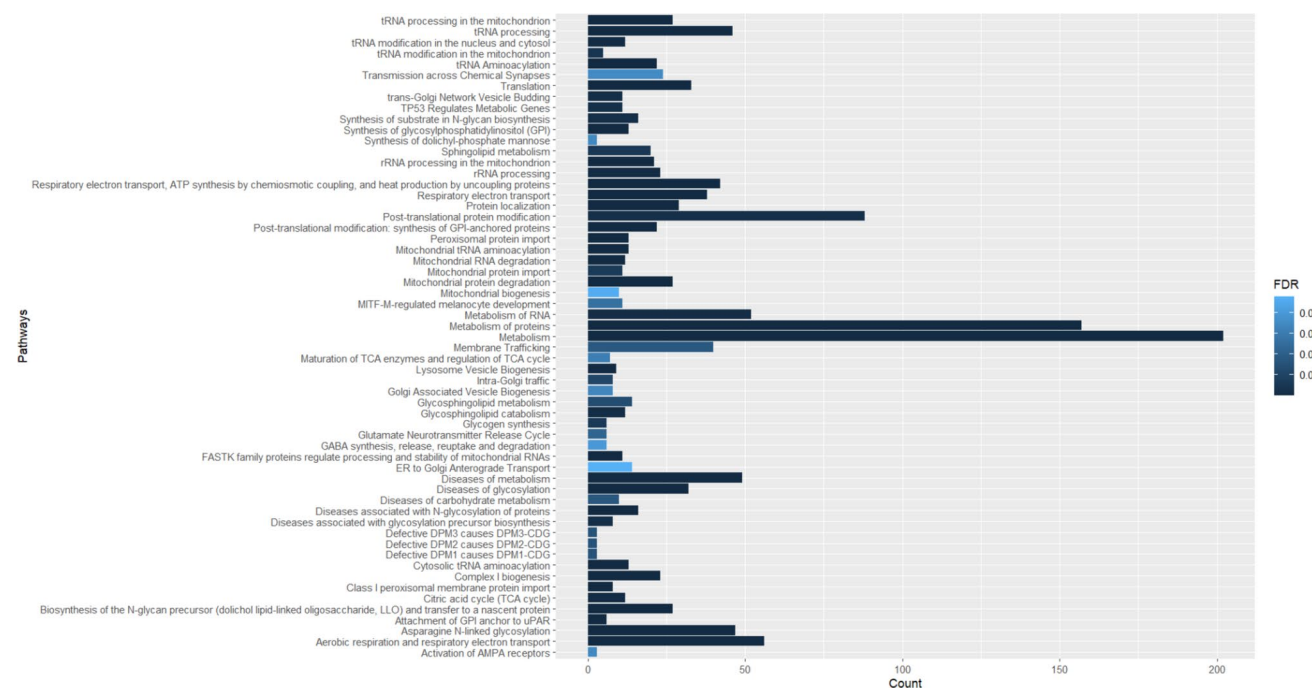ake part in each of pathways. The color bar indicates the FDR, the light blue represents higher value, the dark blue represents lower value

Table 3 Pathways in which the genes associated with treatable metabolic epilepsies take part and their statistical significance

Pathway name	Gene Count	Total Genes in pathway	P-value	FDR
Metabolism of amino acids and derivatives	37	656	$1.11e^{-16}$	$2.48e^{-14}$
Metabolism	80	3,717	$1.11e^{-16}$	$2.48e^{-14}$
Metabolism of vitamins and cofactors	25	391	$1.22e^{-15}$	$1.82e^{-13}$
tRNA processing in the mitochondrion	12	45	$1.35e^{-14}$	$1.50e^{-12}$
Metabolism of water-soluble vitamins and cofactors	20	260	$2.13e^{-14}$	$1.90e^{-12}$
rRNA processing in the mitochondrion	9	40	$1.30e^{-10}$	$9.61e^{-9}$
Defects in vitamin and cofactor metabolism	9	42	$1.98e^{-10}$	$1.25e^{-8}$
PDH complex synthesizes acetyl-CoA from PYR	5	17	$1.23e^{-8}$	$6.77e^{-7}$
Urea cycle	7	32	$1.89e^{-8}$	$9.24e^{-7}$
Regulation of pyruvate dehydrogenase (PDH) complex	6	35	$3.45e^{-8}$	$1.50e^{-6}$
Mitochondrial protein degradation	9	104	$3.75e^{-8}$	$1.50e^{-6}$
Branched-chain amino acid catabolism	8	60	$7.81e^{-8}$	$2.89e^{-6}$
tRNA processing	12	182	$9.37e^{-8}$	$3.19e^{-6}$
MECP2 regulates neuronal receptors and channels	3	32	$4.92e^{-7}$	$1.52e^{-5}$
Regulation of pyruvate metabolism	6	54	$6.26e^{-7}$	$1.77e^{-5}$
Aerobic respiration and respiratory electron transport	13	307	$6.55e^{-7}$	$1.77e^{-5}$
FASTK family proteins regulate processing and stability of mitochondrial RNAs	5	19	$8.84e^{-7}$	$2.12e^{-5}$
Biotin transport and metabolism	5	19	$8.84e^{-7}$	$2.12e^{-5}$
Transcriptional Regulation by MECP2	4	100	$3.47e^{-6}$	$8.00e^{-5}$
Defects in biotin (Btn) metabolism	4	12	$4.56e^{-6}$	$1.00e^{-4}$
Mitochondrial RNA degradation	5	30	$8.03e^{-6}$	$1.69e^{-4}$
Defects in cobalamin (B12) metabolism	5	31	$1.00e^{-5}$	$1.88e^{-4}$
Diseases of metabolism	14	424	$2.52e^{-5}$	$4.66e^{-4}$
Pyruvate metabolism	6	96	$2.59e^{-5}$	$4.66e^{-4}$
Synaptic adhesion-like molecules	4	23	$5.72e^{-5}$	$9.72e^{-4}$
Signaling by Retinoic Acid	5	75	$6.00e^{-5}$	$1.02e^{-3}$
rRNA processing	10	245	$7.00e^{-5}$	$1.11e^{-3}$
Defective HLCS causes multiple carboxylase deficiency	3	10	$1.04e^{-4}$	$1.48e^{-3}$
Unblocking of NMDA receptors, glutamate binding and activation	4	27	$1.06e^{-4}$	$1.48e^{-3}$
Negative regulation of NMDA receptor-mediated neuronal transmission	4	27	$1.06e^{-4}$	$1.48e^{-3}$
Cobalamin (Cbl, vitamin B12) transport and metabolism	5	52	$1.08e^{-4}$	$1.51e^{-3}$
Long-term potentiation	4	31	$1.79e^{-4}$	$2.32e^{-3}$
Cobalamin (Cbl) metabolism	4	33	$2.26e^{-4}$	$2.94e^{-3}$
Respiratory electron transport	7	137	$2.32e^{-4}$	$3.01e^{-3}$
Propionyl-CoA catabolism	3	14	$2.78e^{-4}$	$3.34e^{-3}$
Defective ABCC8 can cause hypo- and hyper-glycemias	2	4	$6.01e^{-4}$	$7.21e^{-3}$
Metabolism of cofactors	5	77	$6.43e^{-4}$	$7.72e^{-3}$
Metabolism of folate and pterines	4	45	$7.22e^{-4}$	$7.94e^{-3}$
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins	7	172	$8.85e^{-4}$	$9.74e^{-3}$
Glycine degradation	3	21	$8.99e^{-4}$	$9.87e^{-3}$
Assembly and cell surface presentation of NMDA receptors	4	49	$9.87e^{-4}$	$9.87e^{-3}$
Cytosolic tRNA aminoacylation	4	57	$1.06e^{-3}$	$1.06e^{-2}$
ATP sensitive Potassium channels	2	6	$1.34e^{-3}$	$1.33e^{-2}$
Creatine metabolism	3	25	$1.48e^{-3}$	$1.33e^{-2}$
Serine biosynthesis	3	25	$1.48e^{-3}$	$1.33e^{-2}$
Glyoxylate metabolism and glycine degradation	4	57	$1.71e^{-3}$	$1.54e^{-2}$
Ras activation upon Ca^{2+} influx through NMDA receptor	3	27	$1.84e^{-3}$	$1.65e^{-2}$
Complex I biogenesis	4	59	$1.94e^{-3}$	$1.75e^{-2}$
Neurexins and neuroligins	4	60	$2.06e^{-3}$	$1.85e^{-2}$
Defective MTRR causes HMAE	2	8	$2.35e^{-3}$	$1.88e^{-2}$
Defective MTR causes HMAG	2	9	$2.96e^{-3}$	$2.36e^{-2}$
tRNA Aminoacylation	4	68	$3.22e^{-3}$	$2.58e^{-2}$
Protein localization	6	171	$4.25e^{-3}$	$3.40e^{-2}$

Table 3 (continued)

Pathway name	Gene Count	Total Genes in pathway	P-value	FDR
Tetrahydrobiopterin (BH4) synthesis, recycling, salvage and regulation	3	37	$4.44e^{-3}$	$3.55e^{-2}$
Synthesis of glycosylphosphatidylinositol (GPI)	3	37	$4.44e^{-3}$	$3.55e^{-2}$
CREB1 phosphorylation through NMDA receptor-mediated activation of RAS signaling	3	39	$5.13e^{-3}$	$3.59e^{-2}$
Vitamin B1 (thiamin) metabolism	2	14	$6.95e^{-3}$	$4.86e^{-2}$

Fig. 4 Pathway analysis of genes associated with non-treatable metabolic epilepsies. y-Axis indicates the pathway name, x-axis indicates the number of genes of interest that take part in each of pathways. The color bar indicates the FDR, the light blue represents higher value, the dark blue represents lower value

database (https://omim.org/) and as a result they are potentially significant in clinical practice (Zhang et al. 2024). Of these genes, 609 are associated with metabolic epilepsies, corresponding to 609 IEMs out of 1904 currently described, according to IEM base (Lee et al. 2018) (Fig. 6).

A key area of interest in current research in epileptology is understanding why some metabolic epilepsies are treatable while others remain refractory to current treatment approaches. This discussion provides an overview of pathway analysis related to treatable and non-treatable metabolic epilepsies, offering insights into their underlying mechanisms and potential therapeutic targets. Pathway analysis offer a comprehensive view of the metabolic processes involved in both treatable and non-treatable forms of metabolic epilepsies. The comparison between these two groups reveals several crucial distinctions in their underlying mechanisms. It is noted that, while pathway names may seem unspecific, they are directly derived from Reactome database, and we maintained them as they are to ensure consistency and accuracy with the database.

The pathway analysis for treatable metabolic epilepsies highlighted the following significant pathways: "Metabolism", "Metabolism of Amino Acids and Derivatives", "Metabolism of Vitamins and Cofactors". Encompassing various metabolic processes, the "Metabolism" pathway is foundational for understanding MDs. The "Metabolism of Amino Acids and Derivatives" pathway includes processes related to amino acid synthesis and catabolism, critical in many treatable metabolic epilepsies, while the "Metabolism of Vitamins and Cofactors" pathway involves the utilization of vitamins and cofactors necessary for cellular function. These pathways suggest that treatable metabolic epilepsies generally involve metabolic abnormalities that can be addressed through targeted therapies, such as enzyme replacement, dietary modification, or specific pharmacological interventions. For instance, biotinidase deficiency, which leads to metabolic epilepsy, is treatable with biotin supplementation, while pyridoxine-dependent epilepsy responds to pyridoxine therapy.

Table 4 Pathways in which the genes associated with non-treatable metabolic epilepsies take part and their statistical significance

Pathway name	Gene Count	Total Genes in pathway	P-value	FDR
tRNA processing in the mitochondrion	27	45	$1.11e^{-16}$	$1.20e^{-14}$
rRNA processing in the mitochondrion	21	40	$1.11e^{-16}$	$1.20e^{-14}$
Complex I biogenesis	23	59	$1.11e^{-16}$	$1.20e^{-14}$
Respiratory electron transport	38	137	$1.11e^{-16}$	$1.20e^{-14}$
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins	42	172	$1.11e^{-16}$	$1.20e^{-14}$
Aerobic respiration and respiratory electron transport	56	307	$1.11e^{-16}$	$1.20e^{-14}$
tRNA processing	46	182	$1.11e^{-16}$	$1.20e^{-14}$
Metabolism of proteins	157	2,345	$1.11e^{-16}$	$1.20e^{-14}$
Metabolism	202	3,717	$7.77e^{-16}$	$7.46e^{-14}$
tRNA Aminoacylation	22	68	$3.11e^{-15}$	$2.70e^{-13}$
Mitochondrial protein degradation	27	104	$6.77e^{-15}$	$5.35e^{-13}$
Diseases of metabolism	49	424	$9.62e^{-13}$	$6.93e^{-11}$
Protein localization	29	171	$4.17e^{-12}$	$2.75e^{-10}$
Diseases of glycosylation	32	202	$1.08e^{-11}$	$6.69e^{-10}$
Diseases associated with N-glycosylation of proteins	16	46	$3.38e^{-11}$	$1.96e^{-9}$
Asparagine N-linked glycosylation	47	431	$6.40e^{-11}$	$3.46e^{-9}$
FASTK family proteins regulate processing and stability of mitochondrial RNAs	11	19	$2.20e^{-10}$	$1.12e^{-8}$
Biosynthesis of the N-glycan precursor (dolichol lipid-linked oligosaccharide, LLO) and transfer to a nascent protein	27	167	$2.90e^{-10}$	$1.39e^{-8}$
Post-translational modification: synthesis of GPI-anchored proteins	22	115	$6.46e^{-10}$	$2.91e^{-8}$
Synthesis of glycosylphosphatidylinositol (GPI)	13	37	$2.08e^{-9}$	$8.54e^{-8}$
Mitochondrial RNA degradation	12	30	$2.08e^{-9}$	$8.54e^{-8}$
Mitochondrial tRNA aminoacylation	13	47	$3.35e^{-8}$	$1.30e^{-6}$
Translation	33	339	$6.97e^{-8}$	$2.58e^{-6}$
Peroxisomal protein import	13	67	$2.95e^{-7}$	$1.06e^{-5}$
Cytosolic tRNA aminoacylation	13	50	$4.96e^{-7}$	$1.69e^{-5}$
Class I peroxisomal membrane protein import	8	20	$1.01e^{-6}$	$3.35e^{-5}$
Attachment of GPI anchor to uPAR	6	10	$2.36e^{-6}$	$7.57e^{-5}$
Lysosome Vesicle Biogenesis	9	43	$5.78e^{-6}$	$1.80e^{-4}$
tRNA modification in the nucleus and cytosol	12	70	$1.46e^{-5}$	$4.40e^{-4}$
Citric acid cycle (TCA cycle)	12	83	$1.67e^{-5}$	$4.83e^{-4}$
rRNA processing	23	245	$1.86e^{-5}$	$5.20e^{-4}$
Glycosphingolipid catabolism	12	78	$4.13e^{-5}$	$1.12e^{-3}$
Metabolism of RNA	52	839	$5.19e^{-5}$	$1.31e^{-3}$
trans-Golgi Network Vesicle Budding	11	80	$5.25e^{-5}$	$1.31e^{-3}$
Synthesis of substrates in N-glycan biosynthesis	16	139	$7.47e^{-5}$	$1.79e^{-3}$
Diseases associated with glycosylation precursor biosynthesis	8	37	$8.13e^{-5}$	$1.95e^{-3}$
TP53 Regulates Metabolic Genes	11	126	$8.63e^{-5}$	$1.98e^{-3}$
Post-translational protein modification	88	1,653	$9.11e^{-5}$	$2.00e^{-3}$
tRNA modification in the mitochondrion	5	14	$1.89e^{-4}$	$4.15e^{-3}$
Sphingolipid metabolism	20	221	$2.52e^{-4}$	$5.29e^{-3}$
Glycogen synthesis	6	24	$2.94e^{-4}$	$6.18e^{-3}$
Mitochondrial protein import	11	70	$3.17e^{-4}$	$6.34e^{-3}$
Intra-Golgi traffic	8	49	$5.27e^{-4}$	$1.05e^{-2}$
Glycosphingolipid metabolism	14	138	$7.08e^{-4}$	$1.34e^{-2}$
Defective DPM1 causes DPM1-CDG	3	5	$8.83e^{-4}$	$1.59e^{-2}$
Defective DPM2 causes DPM2-CDG	3	5	$8.83e^{-4}$	$1.59e^{-2}$
Defective DPM3 causes DPM3-CDG	3	5	$8.83e^{-4}$	$1.59e^{-2}$
Diseases of carbohydrate metabolism	10	81	$9.60e^{-4}$	$1.73e^{-2}$
Membrane Trafficking	40	668	$1.04e^{-3}$	$1.76e^{-2}$
Glutamate Neurotransmitter Release Cycle	6	32	$1.30e^{-3}$	$2.20e^{-2}$
MITF-M-regulated melanocyte development	11	167	$1.54e^{-3}$	$2.62e^{-2}$

Table 4 (continued)

Pathway name	Gene Count	Total Genes in pathway	*P*-value	FDR
Maturation of TCA enzymes and regulation of TCA cycle	7	47	$1.94e^{-3}$	$3.11e^{-2}$
Golgi Associated Vesicle Biogenesis	8	61	$2.09e^{-3}$	$3.34e^{-2}$
Activation of AMPA receptors	3	7	$2.30e^{-3}$	$3.44e^{-2}$
Synthesis of dolichyl-phosphate mannose	3	7	$2.30e^{-3}$	$3.44e^{-2}$
Transmission across Chemical Synapses	24	344	$2.35e^{-3}$	$3.53e^{-2}$
GABA synthesis, release, reuptake and degradation	6	37	$2.66e^{-3}$	$3.99e^{-2}$
Mitochondrial biogenesis	10	129	$3.32e^{-3}$	$4.65e^{-2}$
ER to Golgi Anterograde Transport	14	164	$3.40e^{-3}$	$4.77e^{-2}$
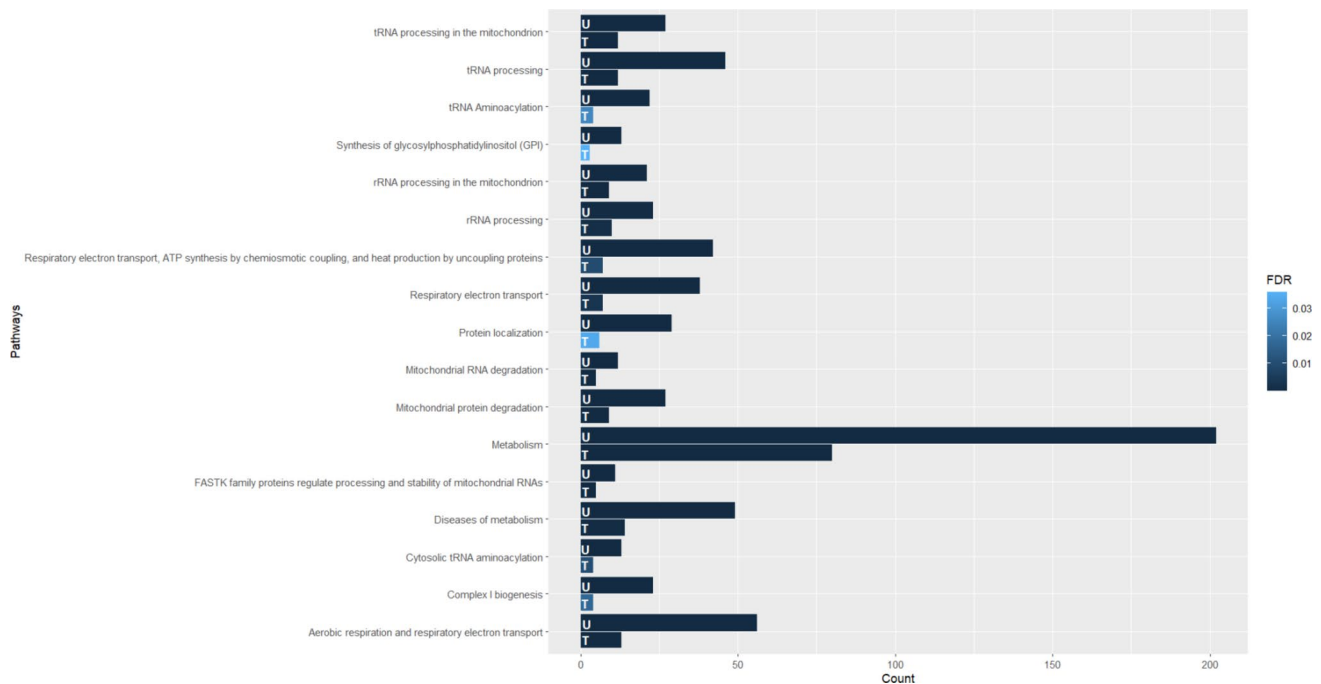
Fig. 5 Common pathways for both treatable and non-treatable metabolic epilepsies. y-Axis indicates the pathway name, x-axis indicates the number of genes of interest that take part in each of pathways. The color bar indicates the FDR, the light blue represents higher value, the dark blue represents lower value. Abbreviations: U-Non-treatable metabolic epilepsies; T-Treatable metabolic epilepsies

In contrast, the pathway analysis for non-treatable metabolic epilepsies showed a broader range of metabolic disruptions, including pathways such as "Metabolism", "Metabolism of Proteins", and "Aerobic respiration and respiratory electron transport". The "Metabolism of proteins" pathway involves protein synthesis and degradation, suggesting more complex disruptions in non-treatable forms. The "Aerobic respiration and respiratory electron transport" pathway is critical for cellular energy production, indicating broader implications in non-treatable metabolic epilepsies. The broader range of pathways in non-treatable metabolic epilepsies points to a higher degree of complexity and potential impact on cellular function. This complexity contributes to the challenges in developing effective treatments for these disorders.

Despite the differences between treatable and non-treatable metabolic epilepsies, the pathway analysis identified several common pathways. Among the 17 common pathways were: "Metabolism", "Diseases of metabolism", "Aerobic respiration and respiratory electron transport". These pathways' involvement in both treatable and non-treatable forms suggests a possible key role in the pathophysiology of metabolic epilepsies. Understanding the differences of these common pathways between treatable and non-treatable metabolic epilepsies may function as a tool to guide future research and develop effective treatments. The complexity of metabolic disruptions rendering a metabolic epilepsy resistant to therapy may be better understood by studying the common pathways and highlighting the differences between drug responsive and resistant forms of metabolic epilepsy.

Table 5 Common pathways for both treatable and non-treatable metabolic epilepsies

Pathway name
Metabolism
tRNA processing in the mitochondrion
rRNA processing in the mitochondrion
Mitochondrial protein degradation
tRNA processing
Aerobic respiration and respiratory electron transport
FASTK family proteins regulate processing and stability of mitochondrial RNAs
Mitochondrial RNA degradation
Diseases of metabolism
rRNA processing
Respiratory electron transport
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins
Cytosolic tRNA aminoacylation
Complex I biogenesis
tRNA Aminoacylation
Protein localization
Synthesis of glycosylphosphatidylinositol (GPI)

Conclusions

The pathway analysis of treatable and non-treatable metabolic epilepsies underscores the complexity and heterogeneity of these disorders. Key differences in metabolic pathways between treatable and non-treatable forms, along with shared pathways, suggest that the specific genetic factors and the roles they play within these pathways largely determine the potential for therapeutic intervention. Treatable metabolic epilepsies often involve disruptions in pathways that can be addressed through targeted therapies, such as enzyme replacement, dietary modification, or specific pharmacological interventions. On the other hand, non-treatable forms are associated with broader and more complex metabolic disruptions, making them refractory to current treatments.

The identification of common pathways across treatable and non-treatable forms indicates potential areas for future research and therapeutic development. Therefore, the genes clustered in these pathways, having been associated with metabolic epilepsies with no effective treatment, could be the first target for further study. Simultaneously, more research both in vivo and in vitro is needed for all those genes known to be associated with non-treatable metabolic epilepsies in order to provide novel insights regarding their therapeutic treatment. This analysis emphasizes the importance of ongoing research to understand the underlying mechanisms of metabolic epilepsies and to develop new targeted therapies for the untreatable forms, ultimately aiming to improve patient outcomes and quality of life.

Declarations

Competing interests The authors declare no competing interests.
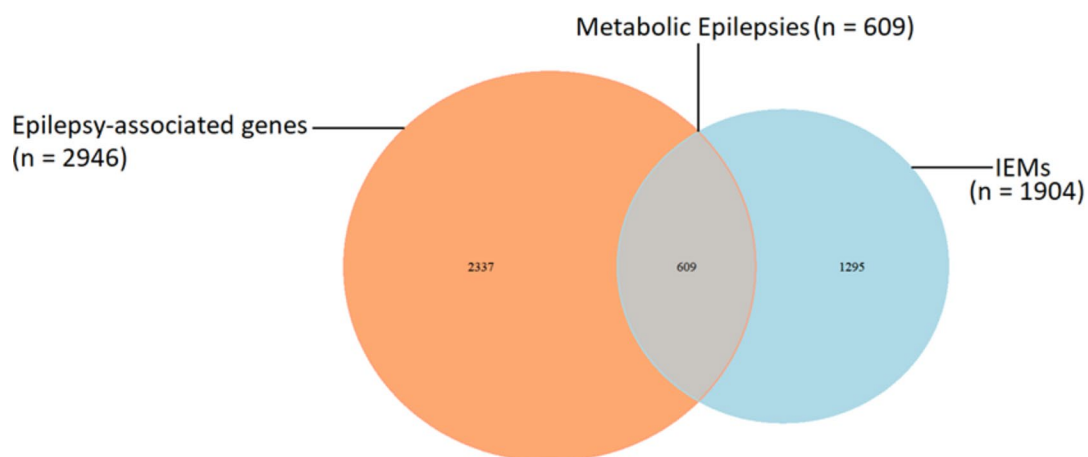
Fig. 6 Comparison of epilepsy-associated genes, IEMs and their overlapping genes

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