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# Rare Inherited Metabolic Disorders with Multisystem Involvement in Pakistan: Molecular Insights and Management Strategies

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**ABSTRACT**

*Inborn errors of metabolism (IMDs), monogenic disorders caused by defects in enzymes, cofactors, or transport proteins, frequently manifest with multisystem involvement and prominent neurological features, including intellectual disability, developmental regression, seizures, ataxia, speech defects, and encephalopathy. Globally, over 1,500 IMDs are recognized, yet only a subset has been documented in Pakistan, likely due to high consanguinity rates (~60–65%), absent national newborn screening, limited diagnostic infrastructure, and under-recognition. This review selectively highlights 20 rare IMDs particularly relevant to the Pakistani population, chosen based on three explicit criteria: (1) documented cases in local registries or publications; (2) frequent or severe neurological phenotypes (e.g., intellectual disability, seizures, regression, dystonia, or ataxia); and (3) elevated prevalence or founder effects in consanguineous cohorts, alongside available epidemiological and genetic data. The selected disorders include galactosemia, phenylketonuria (PKU), cystic fibrosis (CF), tyrosinemia, methylmalonic aciduria (MMA), congenital adrenal hyperplasia (CAH), maple syrup urine disease (MSUD), congenital hypothyroidism, metachromatic leukodystrophy (MLD), Gaucher disease, L-2-hydroxyglutaric aciduria (L2HGA), propionic aciduria (PA), glutaric aciduria type 1 (GA1), multiple carboxylase deficiency (MCD), Niemann-Pick disease (NPD), mucopolysaccharidosis types I and II (MPS I and MPS II), homocystinuria, isovaleric aciduria (IVA), and Wilson disease (WD). We compile recent insights into their genetic etiology (including founder and novel mutations), epidemiology in consanguineous settings, clinical diagnostic challenges (often delayed due to overlapping neurological presentations), and management strategies (dietary modification, cofactor supplementation, enzyme replacement, chelation, and transplantation). Enhanced awareness, expanded selective/high-risk screening, genetic counseling, affordable therapies, and policy support for regional registries and prenatal diagnostics are urgently needed to reduce preventable neurological morbidity and mortality in this high-consanguinity, resource-limited population.*

***Keywords:*** *Inborn errors of metabolism, Pakistan, Protein, Enzymes, Diagnoses.*

## 1. Introduction

It is still unclear which diseases are to be regarded as inherited metabolic disorders (IMDs). Scientists have been fond of referring to inherited (sometimes de novo genetic) defects in the degradation or synthesis of compounds in particular pathways that are typically identified by certain biochemical assays and that are, in some cases, amenable to metabolic therapy. IMDs are multisystem diseases that present inconsistent and progressive clinical patterns [1]. These are mainly related to the full or partial loss of functionality of an individual enzyme, cofactor, or auxiliary protein. IMDs inherently occur either in X-linked or Autosomal recessive mode [2]. Whereas dominant disorder is only present in a small number of disorders, with most of them being related to the biosynthetic metabolic pathway. Recent authoritative sources, including updates to the International Classification of Inherited Metabolic Disorders (ICIMD), indicate a significantly higher number. The ICIMD (initially published in 2021 with 1,450 disorders) continues to evolve, with recent 2024-2025 publications citing 1,564 recognized IMDs (e.g., as per the Metabolic Treatabolome and IEM Knowledgebase review, which identifies 275 treatable IMDs out of 1,564 total as of June 2024) [3]. Other sources confirm figures around 1,450–1,500+ disorders, with some estimates exceeding 1,800 when including emerging or provisional entries [4]. These can be successfully treated if they are suspected and diagnosed early. Treatment can be provided to groups of disorders such as galactosemia, phenylketonuria (PKU), homocystinuria, methylmalonic aciduria (MMA) and congenital hyperammonemia [5–8]. Each of these conditions is not frequent, but taken collectively, they are not uncommon causes of disease during the neonatal period [9, 11]. These IMDs exhibit various patho-mechanisms, such as inadequate supply of cellular energy, loss of reaction product, Accretion of non-metabolized substrates, and Accretion of toxic or harmful substrates and their metabolites, etc., depending on the metabolic functioning of the pathway or biochemical reaction [12, 15]. This review focuses on selected rare inherited metabolic disorders (IMDs) that are either commonly reported in the Pakistani population or particularly relevant due to their variable phenotypes and documented local cases. The selected disorders include galactosemia, phenylketonuria (PKU), cystic fibrosis (CF), tyrosinemia, methylmalonic aciduria (MMA), congenital adrenal hyperplasia (CAH), maple syrup urine disease (MSUD), congenital hypothyroidism, metachromatic leukodystrophy (MLD), Gaucher disease, L-2-hydroxyglutaric aciduria (L2HGA), propionic aciduria (PA), glutaric aciduria type 1 (GA1), multiple carboxylase

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deficiency (MCD), Niemann-Pick disease (NPD), mucopolysaccharidosis types I and II (MPS I and MPS II), homocystinuria, isovaleric aciduria (IVA), and Wilson disease (WD). These were selected based on: (1) availability of published epidemiological or genetic data from Pakistan, (2) frequent presentation with neurological symptoms such as intellectual disability, speech defects, developmental delay, ataxia, seizures, or regression, and (3) potential for early diagnosis and management intervention in resource-limited settings.

## 2. Classification of inherited metabolic disorders (IMDs)

Inherited metabolic disorders (IMDs) are classified into three classes based on

1. Onset of presentation.
2. Pathophysiology
3. Biochemical Pathways [16] (Table 1).

Table 1: Classification of Inherited metabolic disorders (IMDs).

| Classification Basis | Subgroup / Category | Key Examples of Disorders | Typical Clinical Presentation / Hallmarks | Treatability Notes |
|---|---|---|---|---|
| Onset of Presentation | Acute / Intermittent Presentations | Urea cycle disorders Organic acidurias Fatty acid oxidation defects Fructose-1,6-bisphosphatase deficiency Pyruvate dehydrogenase deficiency | Intermittent vomiting, shock, coma, hypoglycemia (often triggered by illness/stress), hyperammonemia, acidosis | Often treatable acutely; many respond to prompt metabolic support |
| | Chronic / Progressive Presentations | Wilson disease GM1 gangliosidosis Fabry disease Mucopolysaccharidoses (severe forms) Metachromatic leukodystrophy | Failure to thrive, developmental delay/regression, hepatomegaly, spastic diplegia, progressive neurological decline | Variable; some treatable (e.g., Wilson), others supportive only |
| Pathophysiology | Intoxication / Accumulation Disorders | Amino acid catabolism defects (e.g., PKU, homocystinuria, MSUD, tyrosinemia) Organic acidurias (e.g., MMA, PA, GA1, IVA) Urea cycle disorders Lysosomal storage disorders Metal intoxication (e.g., Wilson, Menkes) | Acute or chronic intoxication from toxic metabolites; variable acute/chronic presentation | Many highly treatable (diet, chelation, cofactor) if early |
| | Energy Metabolism / Deficiency Disorders | Cytoplasmic (e.g., gluconeogenesis defects, glycogen storage, hyperinsulinism) Mitochondrial (e.g., respiratory chain defects, fatty acid oxidation, Krebs cycle) | Hypoglycemia, lactic acidosis, myopathy, encephalopathy, multiorgan failure | Treatable (e.g., diet, cofactor) in cytoplasmic; often limited in mitochondrial |
| | Complex Molecule / Biosynthesis Disorders | Lysosomal storage disorders Peroxisomal disorders Congenital disorders of glycosylation Inborn errors of cholesterol synthesis | Progressive storage symptoms: organomegaly, dysmorphism, neurodegeneration | Enzyme replacement/substrate reduction available for some LSDs; others supportive |
| Biochemical Pathways | Amino acids & peptides | PKU, homocystinuria, MSUD, tyrosinemia, organic acidurias | Intellectual disability, seizures, encephalopathy, odor, acidosis | Many highly treatable with diet/cofactors |
| | Carbohydrates | Galactosemia, hereditary fructose intolerance, glycogen storage diseases | Hypoglycemia, liver failure, jaundice, cataracts | Highly treatable (dietary restriction) |
| | Fatty acids & ketone bodies | Fatty acid oxidation defects, ketone body defects | Hypoglycemic coma, cardiomyopathy, myopathy | Treatable with frequent feeding, medium-chain triglycerides |
| | Energy metabolism (mitochondrial) | Respiratory chain defects, pyruvate metabolism defects | Lactic acidosis, multiorgan failure, neurodegeneration | Often limited; cofactor trials in some |
| | Lysosomes & peroxisomes | Mucopolysaccharidoses, sphingolipidoses, peroxisomal disorders | Organomegaly, dysmorphism, progressive neurodegeneration | ERT/HSCT for some; mostly supportive |
| | Metals & trace elements | Wilson disease, Menkes disease | Neurological deterioration, liver failure, connective tissue issues | Highly treatable (chelation/zinc) |

## 3. Inheritance of inherited metabolic disorders (IMDs)

Knowing the inheritance pattern is very important for the proper diagnosis of the disease. In addition to helping the family with genetic counselling to prevent the disease from spreading further, a family record spanning at least 3 generations is useful for precise identification of the illness [17]. Genetic disorders are inherited in all possible patterns. Table 2 shows the details of the inheritance pattern with a suitable example.

Table 2: Inheritance pattern of inherited metabolic disorder (IMDs).

| Type of Inheritance | Key Characteristics | Common Examples | Relevance in Pakistan |
|---|---|---|---|
| Autosomal Recessive | Both alleles affected; affects siblings; generation gaps; consanguinity common; males/females equally affected | Crigler-Najjar syndrome, Wilson disease, most mucopolysaccharidoses (except Hunter), galactosemia, phenylketonuria | Highly relevant due to high consanguinity (~60–65% of marriages, often first-cousin) |
| Autosomal Dominant | One allele sufficient; no generation gap; multiple generations affected; males/females equal | Acute intermittent porphyria, familial hypercholesterolemia | Less common in recessive-heavy IMD burden |
| X-linked | No father-to-son transmission; through carrier mothers; daughters of affected fathers are carriers; 50% risk for sons of carrier mothers | Hunter syndrome (MPS II) | Variable; less dominant in consanguineous populations |
| Mitochondrial | Maternal transmission; affects sons/daughters equally; no father-to-son | Leigh disease, Kearns-Sayre syndrome | Rare in reported Pakistani IMD cases |

## 4. Epidemiology of inherited metabolic disorders (IMDs) in Pakistan.

In Pakistan, the cousin marriages are about 63 percent, among which 84.0 percent of marriages are said to be between first cousins [18, 19]. It has high consanguinity and high family size, which has made it a perfect population to study genetic disorders that are autosomal in nature [20]. This is because the elevated prevalence of various genetic syndromes in Pakistan endorses the elevated rate of cousin marriages [21]. It is a challenge to obtain the data of IMDs in the Pakistani Population because there are no appropriate clinical records, and IMDs are discussed as a very rare disease [22, 24]. There is evidence of a higher prevalence of carbohydrate disorders than lysosomal storage disorders, with frequencies of 51 and 32.7, respectively [25, 28]. Although the less common of them were amino acid metabolism disorders, organic acids and energy metabolism disorders, lysinuric protein intolerance, neonatal hemochromatosis, and bile acids synthesis defect [29]. General information on GM1 gangliosidosis, Wilson syndrome, and inherited unconjugated hyperbilirubinemias in Pakistan is not available. MPS-1 with a frequency of 83-3% was found as the most prevalent, with another study on the prevalence of mucopolysaccharidoses, followed by MPS-IV with a frequency of 6.67, MPS-III with a frequency of 5.5.6, and MPS-II syndrome [30]. The WHO has identified Pakistan as one of the 57 nations in the world that have severe shortages of health care employees [31]. Pakistan has approximately 0.8 physicians to 1000 people compared to 2.4 in America [32, 33]. In Pakistan, the mandate of the province government mostly governs the role of the health care organization. However, the federal government has control of the planning of national health strategies [34, 37].

## 5. Status of Inherited Metabolic Disorders (IMDs) in Pakistan.

Mortality rates of infants and children under five of children, in Pakistan are 74/1000 and 89/1000 live births, respectively [38]. Birth asphyxia, neonatal tetanus pneumonia, still birth, sepsis, diarrhea, and congenital birth defects are recognized as main causes of neonatal and infant death in less developed countries [39, 40]. IMDs have been largely disregarded by the government, in part because of the attention devoted to these issues.

Basic metabolic testing has been available for decades. Though little has developed until recently, there is little in clinical practice to aid the identification and management of patients, especially the newborn child with IMDs [41, 45]. Management of IMDs with food for special medical purposes (FSMP) and the availability of orphan drugs are problematic [46], creating a cumbersome position for physicians and families. Most cases are left unidentified and result in irreversible psychomotor retardation or death.

The persistently high consanguinity rate in Pakistan (~61–65%) of marriages, predominantly first-cousin unions; recent 2025 Population Council analysis and demographic studies) markedly increases the prevalence of autosomal recessive IMDs [10, 11, 47, 48]. However, the complete absence of a mandatory national newborn screening program, reliance on selective/hospital-based testing, limited metabolic expertise, and restricted access to orphan drugs/specialized nutrition result in late or missed diagnoses, irreversible neurological damage, and preventable morbidity/mortality. These structural and resource-related challenges form the central unmet needs addressed in this review [49, 56].

### *5.1 Preventive Strategies: Prenatal Diagnosis and Genetic Counseling*

Consanguinity remains the dominant driver of autosomal recessive IMDs in Pakistan. Preventive approaches—such as prenatal diagnosis (via chorionic villus sampling or amniocentesis) and accessible genetic counseling integrated into antenatal and primary care, offer substantial potential to reduce recurrence risks [57, 61]. Informed reproductive choices that respect social norms could be encouraged through culturally sensitive education, community-based carrier screening, and connections to current maternal-child health programs. These tactics are high-impact, reasonably priced public health interventions in high-consanguinity settings, despite the fact that their implementation necessitates investments in public awareness, laboratory infrastructure, and training.

## 6. Clinical tests for the diagnosis of inherited metabolic disorders (IMDs)

Clinical manifestations that helped to suspect and diagnose are shown in Table 3

Table 3: Tests and therapies for inherited metabolic disorders (IMDs).

| Group / Disorder | Key Initial Tests (Basic) | Confirmatory Tests | Availability in Pakistan | Notes / Challenges |
|---|---|---|---|---|
| Phenylketonuria (PKU) | Plasma amino acids (elevated phenylalanine (Phe)) | PAH sequencing, BH4 loading test | Plasma amino acids available in select centers (tandem MS) | No national NBS; delayed diagnosis common |
| Maple Syrup Urine Disease (MSUD) | Plasma branched-chain amino acids (BCAAs), urine odor | BCKD gene panel | Plasma amino acids available in select centers | Urgent dialysis needed in crises |
| Tyrosinemia Type I | Plasma Tyr, urine succinylacetone | FAH sequencing | Specialized labs only | Rare testing; nitisinone access limited |
| Homocystinuria | Plasma homocysteine (Hcy)/ methionine (Met) | CBS sequencing, enzyme assay | Plasma Hcy widely available | Pyridoxine-responsive cases |
| Methylmalonic Aciduria | Plasma acylcarnitines (C3 acylcarnitine), Urine organic acids (UOA), ammonia | MUT sequencing, B12 response | Acylcarnitine and organic acid profiling in tertiary labs | Common in consanguineous; tertiary labs |
| Propionic Aciduria | Acylcarnitines (C3), UOA | PCCA/PCCB sequencing | Acylcarnitine profiling in tertiary labs | High in hospital cohorts |
| Glutaric Aciduria Type 1 | Acylcarnitines (C5DC), UOA | GCDH sequencing, brain MRI | Acylcarnitines and MRI in tertiary centers | Striatal necrosis characteristic |
| Multiple Carboxylase Deficiency | UOA, acylcarnitines (C5OH) | Biotinidase assay, BTD/HLCS sequencing | Organic acids available; biotin trial diagnostic | Biotin-responsive; excellent if early |
| Isovaleric Aciduria | Acylcarnitines (C5), UOA | IVD sequencing | Acylcarnitine and organic acid testing in labs | Good prognosis if early |
| Metachromatic Leukodystrophy | Urine sulfatides, nerve conduction | ARSA enzyme assay, sequencing | Enzyme assay in reference labs | MRI white matter changes key |
| Gaucher Disease | Chitotriosidase, glucocerebrosidase assay | GBA sequencing, bone marrow | Enzyme and chitotriosidase testing in select centers | ERT access limited |
| Niemann-Pick Disease (esp. Type C) | Chitotriosidase, bone marrow (foam cells) | Sphingomyelinase assay, NPC1/2 sequencing | Chitotriosidase testing in select centers | Miglustat for Type C |
| Mucopolysaccharidosis Type I (MPS I) | Urine glycosaminoglycans (GAGs) | IDUA enzyme assay, sequencing | Urine GAGs screening; enzyme in tertiary labs | Most common MPS (83%) |
| Mucopolysaccharidosis Type II (MPS II) | GAGs | IDS enzyme assay, sequencing | Urine GAGs available; enzyme testing limited | X-linked; less common |
| Galactosemia | Urine reducing substances, blood glucose | Beutler test (GALT activity), GALT sequencing | Urine and basic blood widely available; enzyme/genetic testing limited | Selective screening; limited genetic labs |
| Cystic Fibrosis | Sweat chloride, immunoreactive trypsinogen | CFTR gene panel | Sweat test available in major hospitals; genetic testing limited | Underrecognized; expensive mutation testing |
| Congenital Adrenal Hyperplasia | 17-OH progesterone, electrolytes | CYP21A2 analysis, ACTH stimulation | 17-OHP testing available in major hospitals | Salt-wasting crises prompt urgent testing |
| Congenital Hypothyroidism | TSH, free T4 | Thyroid ultrasound/scintigraphy | TSH and free T4 widely available | ~1:1000; no routine NBS |
| L-2-Hydroxyglutaric Aciduria | Urine/plasma/CSF L-2-HG | L2HGDH sequencing | Organic acid analysis in specialized labs | Novel mutations reported locally |
| Wilson Disease | Serum ceruloplasmin (CP), 24-h urine copper | ATP7B sequencing, slit-lamp KF rings | CP and urine copper widely available | Kayser-Fleischer rings diagnostic clue |

## 7. The most common inherited metabolic disorders in Pakistan.

Several inherited metabolic conditions have been documented across various regions of Pakistan, reflecting the genetic diversity and high consanguinity rates within the population [62, 66]. These disorders often present early in life and manifest through complex neurological and systemic symptoms, underscoring the need for improved screening and genetic counseling programs [67, 74]. The following section presents the 20 selected inherited metabolic disorders grouped thematically according to their primary pathophysiological and biochemical mechanisms: amino acid and related disorders, organic acidurias, lysosomal and storage disorders, other metabolic and endocrine disorders, and metal and miscellaneous disorders. This organization highlights shared clinical patterns, particularly prominent neurological manifestations such as intellectual disability,

seizures, encephalopathy, dystonia, and regression, as well as common diagnostic approaches, treatment principles, and consanguinity-driven prevalence in the Pakistani population. By clustering disorders with overlapping metabolic pathways and clinical phenotypes, the discussion shifts from a sequential listing to a more analytical framework, facilitating comparison of local epidemiological trends, diagnostic challenges in resource-limited settings, and opportunities for early intervention in treatable conditions. Summary characteristics of each disorder are provided in Tables 4, 6, and 7 for quick reference.

### *7.1 Group A: Amino Acid & Related Disorders (4 disorders)*

#### *7.1.1 Phenylketonuria (MIM: 261600).*

Phenylketonuria (PKU) is an inborn metabolic disorder that is caused by the homozygous mutation of the *PAH* gene, leading to a deficiency of the enzyme phenylalanine hydroxylase (PAH) [75]. PAH mutation leads to a lack of PAH, which plays a vital role in the hydroxylation of Phe into Tyr [76, 79]. It is a phenylalanine catabolic disorder [80, 81]. Typical clinical phenotypes comprise cognitive development disorder postnatally, severe pigmentation, gait and stance as well as sitting posture anomalies, cutaneous eczematous, and epilepsy [82–84]. In an investigation established via newborn screening rates in the West Midlands in England, the incidence of PKU did not significantly differ between Pakistani and white children (0.7/10,000 vs 0.8/10,000), but the frequency of the gene in the Pakistani people was significantly lower [85, 86]. Diagnostic tests on PKU are conducted to examine the presence of harmful amounts of acids and toxins in the body. i.e., PAA (Plasma Amino Acid), urine and/or blood, CSF neopterin and biopterin tests, and also physical examination to examine fundamental characteristics of PKU [87, 90]. Treatment and medication include, sapropterin (Kuvan) (recently granted by the FDA USA), fish oil, and BH4 supplements etc [91, 95]. Figure 1 shows the Phenylpropanoid Biosynthesis Pathway.

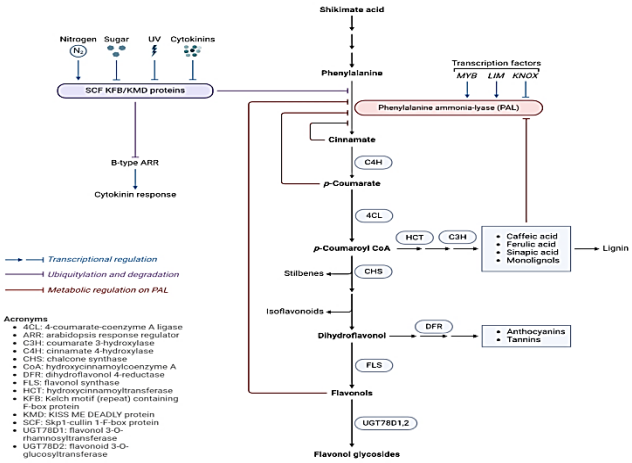


Fig.1: Phenylpropanoid Biosynthesis Pathway [96]

#### 7.1.2 Maple Syrup Urine Disease (MIM: 248600).

Maple syrup urine disease (MSUD) results from a deficiency of the branched-chain alpha-keto acid dehydrogenase complex (BCKDC) can be caused by a homozygous or compound heterozygous mutation in three known genes, i.e., *BCKDHA* [97], *BCKDHB*, and *DBT* [98,99]. These genes encode for two of the catalytic elements of the *BCKDC*, which is involved in the breakdown of the three BCAAs, i.e., isoleucine (Ile), leucine (Leu), and valine (Val). Major clinical symptoms include vomiting, loss of energy (lethargy), and developmental delay. If not treated, maple syrup urine disease can result in seizures, coma, and death [100, 102]. In the whole world, Maple syrup urine disease occurs in 1 in 185,000 babies. In Pakistan, the prevalence is estimated at 1:385, USA 1:225, and 1,016 in the UK [103, 105]. The identification test involves the ketonuria test, plasma amino acids, urine test, and enzyme activity test, etc. Figure 2 shows the condition of health with urine color.

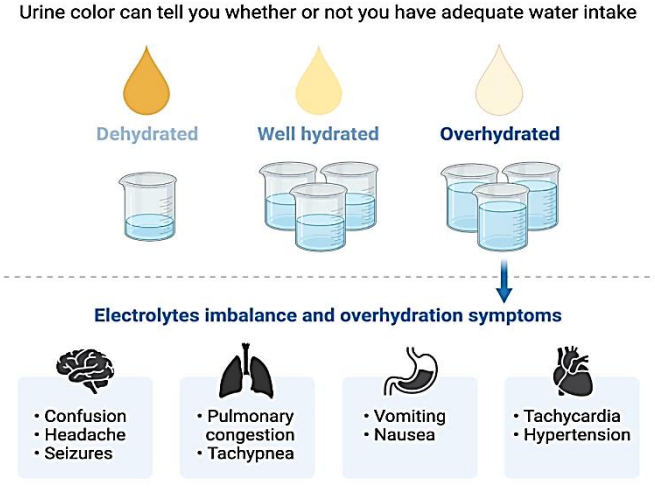


Fig. 2: Urine Color to identify your health [106].

#### *7.1.3 Tyrosinemia (MIM: 276600).*

It is an inherited disorder that is marked by interruptions in a multistep process that breaks down Tyr [107, 114]. It is of three types, that is, tyrosinemia type I (TYRSN1; MIM 276700) is brought about by a homozygous, or compound, mutation in the *FAH* gene [115, 117]. The final enzyme of the Tyr catabolic pathway is the enzyme fumarylacetoacetate hydrolase (FAH). Mutation of the *TAT* gene causes tyrosinemia type II (TYRSN2; MIM 276600) [118, 121]. The *HPD* gene mutation causes tyrosineamia type III (TYRSN3; MIM 276710) and is converted to 4-hydroxyphenylpyruvate by the liver-specific enzyme, tyrosine aminotransferase (TAT) [122]. 4-Hydroxyphenylpyruvate dioxygenase, which converts 4-hydroxyphenylpyruvate to homogentisate, is a part of the catabolic pathway of diarrhea and bloody stools, vomiting, poor weight gain, extreme sleepiness, irritability, liver disease, and kidney diseases [123]. Pakistan has fewer documented studies of this disorder. Globally, tyrosinemia

type I has a predominance of roughly 1/100000. Diagnosis tests such as quantitative plasma amino acid analysis [124], urine organic acid analysis, and mutation analysis and sequencing of reported genes. Possible treatment incorporates a low-phenylalanine, low-tyrosine diet [125], a drug, i.e., nitisone or NTBC [126, 128].

*7.1.4 Homocystinuria (MIM: 236200)*

Homocystinuria is an autosomal recessive amino acid disease caused mainly by mutations in the *CBS* gene, which makes Hcy-based metabolism ineffective, leading to the accumulation of Hcy [129]. It is characterized by ectopia lentis, marfanoid habitus, thromboembolism, osteoporosis, intellectual disability, seizures, and psychiatric problems. Its rates are highest in the Pakistani cohort (2.1% intellectually disabled), and worldwide the rates are 1: 200,000-335,000, but in Pakistan are elevated because of consanguinity [130, 131]. There are mutations such as p.Thr191Met (which is common in certain studies); global hotspots such as p.Gly307Ser. Diagnosis is made by plasma amino acids (increased Hcy/Met), CBS assay, and sequencing. Therapy incorporates pyridoxine (forms of B6-responsible), a methionine-restricted diet, betaine, and folate/B12; early diagnosis helps to avoid vascular/neurological problems [132].

*7.2 Group B: Organic Acidurias (5 disorders)*

*7.2.1 Methylmalonic Aciduria due to Methylmalonyl-CoA Mutase Deficiency (MIM: 251000).*

Methylmalonic aciduria results from a deficiency in methylmalonyl-CoA mutase (MUT), causing methylmalonic aciduria (MMA); an autosomal recessive disorder of methylmalonate metabolism and cobalamin (Vitamin B12) metabolism, and a breakdown of methylmalonyl-CoA to succinyl-CoA (Suc-CoA). MMA arises from either a homozygous mutation in the *MUT* gene or a compound heterozygote [133]. Variable clinical features arise, such as it can be benign to as serious as fatal neonatal phenotypes. Clinical features in more severe conditions are cardiac, renal, neurological, liver, and developmental delays, which may or may not be the same in every person [134, 135]. The incidence of methylmalonic acidemia (MMA) is estimated to range between 1 in 50,000 and 1 in 100,000 live births in the United States; however, its prevalence in Pakistan has not yet been documented. Diagnostic evaluation for MMA may include assessment of ammonia levels, blood gas analysis, complete blood count, brain imaging through CT scan or MRI, measurement of electrolyte levels, genetic testing, methylmalonic acid and cobalamin disorder panels, and plasma amino acid profiling [136].

The use of antibiotics, monitored diet (avoid specific fats and amino acids), and transplant of the kidney and liver are treatment methods since the transplanted organs will provide the body with new cells that can aid in the metabolism of methylmalonic acid in the normal way.

*7.2.2 Propionic Aciduria (MIM: 606054)*

Propionic aciduria (PA) is an autosomal recessive organic acidemia caused by homozygous or compound heterozygous mutations in the *PCCA or PCCB* genes, encoding subunits of propionyl-CoA carboxylase (PCC)[137, 139].

This enzyme deficiency impairs the catabolism of BCAAs, odd-chain fatty acids, and cholesterol, leading to the accumulation of propionic acid and related metabolites. Clinical phenotypes vary from neonatal-onset with severe metabolic acidosis, hyperammonemia, lethargy, vomiting, seizures, and encephalopathy to later-onset forms with intermittent decompensations triggered by infections or protein intake. Long-term complications include developmental delay, intellectual disability, cardiomyopathy, pancreatitis, and optic neuropathy [140]. PA is more common in hospital-based cohorts (e.g., 3–9% of organic acidemias in tertiary centers like Karachi) and is commonly reported in consanguineous families in Pakistan. The prevalence is thought to be between 1:50,000 and 150,000 live births worldwide, but selective screening in high-risk Pakistani populations indicates a higher incidence (up to 62% of organic acidemias in some studies), which is probably underestimated because newborn screening is lacking. Urine organic acids (elevated 3-hydroxypropionate, methylcitrate, and propionylglycine), plasma acylcarnitines (elevated C3-carnitine), and *PCCA/PCCB* gene sequencing are examples of diagnostic tests [141, 142]. Early intervention prevents neurological damage. Treatment includes a protein-restricted diet, metronidazole (to reduce gut propionate production), carnitine supplementation (to conjugate propionyl groups), and liver transplantation in severe cases [143, 144].

*7.2.3 Glutaric Aciduria Type 1 (MIM: 231670)*

Glutaric aciduria type 1 (GA1) is an autosomal recessive disease caused by homozygous or compound heterozygous mutations in the *GCDH* gene, causing the deficiency of glutaryl-CoA dehydrogenase (GCDH) [145]. This interferes with the lysine, hydroxylysine, and tryptophan metabolism, resulting in the accumulation of glutaric acid, 3-hydroxyglutaric acid, and glutaconic acid neurotoxins. Clinical presentation Clinical manifestations consist of macrocephaly at birth, which is subsequently followed by acute encephalopathic crises (usually triggered by illness) and include dystonia, seizures, hypotonia, and regression of development; untreated cases result in severe movement disorders that resemble cerebral palsy [146, 150]. GA1 is one of the more prevalent organic acidurias in consanguineous groups of Pakistan (e.g., 24% in certain high-risk screenings), with a prevalence of approximately 1:100,000 live births worldwide, but greater local prevalence because of founder effects. C.242C>T (p.Trp81Leu) and c.427G>A (p.Val143Ile) have been reported in Pakistani patients. Diagnostic approaches involve urine organic acids (elevated glutaric/3-hydroxyglutaric acids), plasma acylcarnitines (elevated C5DC), brain MRI (striatal necrosis,

frontotemporal atrophy), and GCDH sequencing. Management includes lysine/tryptophan-restricted diet, carnitine/riboflavin supplementation, and aggressive treatment of intercurrent illnesses to prevent crises; newborn screening enables presymptomatic therapy[151, 153].

*7.2.4 Multiple Carboxylase Deficiency (MIM: 253270/253260)*

Multiple carboxylase deficiency (MCD) is an autosomal recessive biotin-responsive disease that occurs due to a mutation in the genes of holocarboxylase synthetase (*HLCS*) deficiency or biotinidase (*BTD*) deficiency, which interferes with the ability of biotin to bind carboxylases that play a role in gluconeogenesis, fatty acid synthesis, and metabolism of amino acids [154, 155]. It has symptoms such as metabolic acidosis, hypotonia, seizures, alopecia, dermatitis, developmental delay, and immune dysfunction; the untreated cases proceed to coma or even death [156, 158]. MCD is a common problem in consanguineous populations in Pakistan (7-8% of IMDs in registries), where incidence is 1:40,000-100,000 worldwide, but 1:2,000 in Pakistan because of consanguinity. BDT variants that are frequent in Pakistani cohorts are c.98_104delinsTCC (p.Cys33Phefs), c.1612C>A (p.Arg538Ser), and c.1330G>C (p.Asp444His). Diagnosis is based on urine organic acids (elevated 3-hydroxyisovalerate, lactate), plasma acylcarnitines (elevated C5OH), biotinidase assay, and gene sequencing [159]. Oral biotin (5-20 mg/day) is effective, and the symptoms usually disappear as soon as treatment begins; timely diagnosis of the disease through the newborn screening program eliminates irreversible neurological consequences.

*7.2.5 Isovaleric Aciduria (MIM: 243500)*

Isovaleric aciduria (IVA) is an autosomal recessive organic acidemia from *IVD* gene mutations, causing isovaleryl-CoA dehydrogenase deficiency and isovaleric acid buildup. Neonatal form is exhibited by the odor of sweaty feet, acidosis, vomiting, lethargy, seizures; chronic forms are failure to thrive and sporadic crises [160, 161]. IVA is observed in high-risk screenings in Pakistan (3-4% of organic acidemias) with a worldwide prevalence of 1:100,000-250,000. Such mutations as p.Arg398Gln have been reported locally [162, 165]. Diagnosis is based on urine organic acids (isovalerylglycine), plasma acylcarnitines (C5), and IVD sequencing. Management includes dietary Leu restriction, a combination of glycine/carnitine, and management of the crisis, prognosis has been reported to be very good in case of early diagnosis [166, 167].

*7.3 Group C: Lysosomal & Storage Disorders (5 disorders)*

*7.3.1Metachromatic Leukodystrophy (MIM: 250100).*

Metachromatic leukodystrophy (MLD) is an autosomal recessive condition due to a pathogenic mutation in the *ARSA* gene, which results in the deficiency of the enzyme arylsulfatase A (ARSA) in the body. MLD is characterized by an elevated concentration of cerebrospinal fluid [168]. Also, the affected individual presents with the metachromatic galacto-sphingo-sulfatile content found in excess white matter of the central nervous system, urinary sediment, and also the kidney [169, 171]. MLD is an incredibly rare disorder with a prevalence of 1-9 individuals out of a population of 1,000,000 worldwide [172, 174]. The clinical features of MLD include optic atrophy, mental deterioration, loss of speech, hypotonia, muscle weakness, gait, hyporeflexia, dysarthria, dystonia, chorea, ataxia, spastic tetraplegia, hyperreflexia (later), seizures, and bulbar palsies [175, 176]. MLD can be misdiagnosed as a range of psychological conditions i.e., blood test, urine testing, and imaging studies. The main possible treatment for MLD includes umbilical cord blood or bone marrow transplant [177, 181].

7.3.2 Gaucher Disease (MIM: 230800).

Gaucher disease is a genetic condition that arises from homozygous or compound heterozygous mutations in the *GBA* gene, which codes for the enzyme, acid β-glucosidase (GBA). This genetic condition is classified as a lysosomal storage disease and is characterized by insufficient activity of beta-glucocerebrosidase [182]. Gaucher disease can be classified into three forms: Gaucher disease Type I, Gaucher disease Type II, and Gaucher disease Type III. All three types are autonomous due to a mutation in the *GBA* gene, but they do present some differences in their respective phenotypes [183, 185]. Common symptoms include 'Gaucher' cells in the bone marrow, hypersplenism, thrombocytopenia, anemia, pancytopenia, hyperpigmented skin lesions, osteonecrosis, pathological fractures, and bone pain (bone crises). In Pakistan, the prevalence of Gaucher disease is still unknown, as it is a rare metabolic disorder. The preferred laboratory diagnostic test is a blood test for the activity of the lysosomal enzyme. Approved treatments are available to help manage the disorder; however, there is no cure for it at this time. These treatment options include Enzyme replacement therapy (ERT) and hematopoietic stem cell transplantation (HSCT) [186, 189].

*7.3.3 Niemann-Pick Disease (MIM: 607616 for A/B; 257220 for C)*

Niemann-Pick disease (NPD) includes lysosomal storage diseases: type A/B (acid sphingomyelinase deficiency, SMPD1 mutations), including the accumulation of sphingomyelin, and type C (*NPC1/NPC2* mutations), including the accumulation of cholesterol [190, 191]. Severe infantile neurodegeneration type A; type B is hepatosplenomegaly and pulmonary; type C is progressive ataxia, dystonia, vertical supranuclear gaze palsy, seizures, and cognitive impairments [192, 194]. NPD is widespread in Pakistani genomic research (e.g., 5-10% of LSDs), and the world prevalence is 1:100, 000250,000, however local prevalence is high. In 20 Pakistani patients, SMPD1 mutations have been reported to be of five variants (e.g., novel frameshifts and missense mutations). Diagnosis involves chitotriosidase test, bone marrow biopsy (foam cells), filipin staining (in NPC), enzyme (sphingomyelinase), and gene sequencing [195, 197]. Treatment is helpful (e.g., miglustat in NPC to stabilize neurology); enzyme

replacement (olipudase alfa) in A/B is promising; genetic counseling is essential in high-consanguinity studies [198].

### *7.3.4 Mucopolysaccharidosis Type I (MPS I, Hurler Syndrome or Variants) (MIM: 607014)*

Mucopolysaccharidosis type I (MPS I) is an autosomal recessive lysosomal disorder due to mutations in the *IDUA* gene, causing α-L-iduronidase deficiency and glycosaminoglycan (dermatan/heparan sulfate) accumulation [199]. Coarse facial features, skeletal dysplasia, hepatosplenomegaly, heart problems, and neurocognitive decline are features of the severe (Hurler) form; milder (Scheie) forms preserve intellect. Due to consanguinity, MPS I accounts for 83% of MPS cases in Pakistani registries, with a global prevalence of 1 in 100,000. c.1469T>C (p.Leu490Pro), c.784delC (p.His262Tyrfs*55), c.908T>C (p.Leu303Pro) and c.1172_1173insGCTGCTGGC are examples of common mutations. IDUA enzyme assay, sequencing, and urine GAGs (elevated dermatan/heparan sulfate) are used in the diagnosis process [200, 202]. Hematopoietic stem cell transplantation (for severe forms), enzyme replacement therapy (laronidase), and supportive care are all part of the treatment; early intervention stops progression [203, 204].

### *7.3.5 Mucopolysaccharidosis Type II (MPS II, Hunter Syndrome) (MIM: 309900)*

Mucopolysaccharidosis type II (MPS II) is a genetic disease caused by mutations in the *IDS* gene (iduronate-2-sulfatase), resulting in the lack of glycosaminoglycan catabolism and deposition of GAGs. Symptoms resemble those of MPS I (coarse features, skeletal problems, organomegaly), but there is behavioral hyperactivity and less corneal clouding; the most severe forms lead to neurodegeneration [205]. In Pakistan, MPS II occurs less frequently (1-5 percent of MPS), but in consanguinity families, and the prevalence in the population is 1:100,000-170,000 males worldwide [206]. Reported locally c.353T>A (p.Leu118Ter) novel mutations. Urine GAGs, IDS enzyme assay (low in men, inconsistent in women), and sequencing are used in diagnosis. The treatment needs enzyme replacement (idursulfase), supportive therapies, and trials of gene therapy; carrier screening is recommended in at-risk families [207].

## *7.4 Group D: Other Metabolic / Endocrine Disorders (4 disorders)*

### *7.4.1 Galactosemia (MIM: 230440).*

Galactosemia is a metabolic condition, inherited in a recessive manner by a homozygous/compound heterozygous mutation in the *GALT* gene [208]. When a mutation occurs in *GALT*, the enzyme required for the metabolism of galactose, galactose-1-phosphate uridylyltransferase (GALT), is dysfunctional. It is classified as a galactose metabolism disorder [209, 211]. In Long-term problems, neonates who are affected by the condition show symptoms of jaundice, liver cell insufficiency, hepatosplenomegaly, intolerance to food, renal tubular dysfunction, hypoglycemia, sepsis, hypotonia, and cataract after taking galactose. include verbal dyspraxia, motor dysfunction, hypergonadotropic hypogonadism, and intellectual delay [212]. In regions with screening programs, incidence at birth appears to be 2.6 times higher in these regions. Prevalence rates are projected to be 1 in 30,000-60,000 live births [213, 223]. In Pakistan, the ratio of galactosemia is 1:9634 [224, 225]. Diagnostic test of galactosemia consists of the urine test for the presence of galactosemia, the Beutler test, used to screen for galactosemia by determining the concentration of the enzyme GAL-1-PUT in the newborn's Urine. The GALT test is used to screen galactosemia by measuring the concentration of the enzyme GAL-1-PUT in the newborn's Blood [226, 229]. Physiological tests are used to test the physical manifestation and symptoms of Glucosemia, and genetic test are used to identify the causative mutation in the *GALT* gene [230, 232]. Therapy involves taking Galactose-free and lactose-free food and avoiding milk and food containing this ingredient [226, 233, 236].

### *7.4.2 Cystic Fibrosis (MIM: 219700).*

Cystic Fibrosis (CF) is caused by a homozygous or compound heterozygous mutation in the *CFTR* gene. Virtually all CF males are infertile because of the bilateral congenital absence of the vas deferens [237, 238]. The level of sodium chloride in the sweat of the affected individuals is high, and a concentrated amount of immunoreactive trypsinogen (IRT) in the neonatal serum is also high (figure 3) [239,240]. Pancreatic insufficiency is also known to be prevalent in the Pakistani population [241]. Pulmon diagnostic test, i.e., includes sweat test, immunoreactive trypsinogen test (IRT), and mutation investigation of the *CFTR* gene [242]. Potential treatment consists of antibiotics, anti-inflammatories, bronchodilators, mucolytic pharmaceuticals, vitamins, and medications, a high-and calorie diet [243, 245].

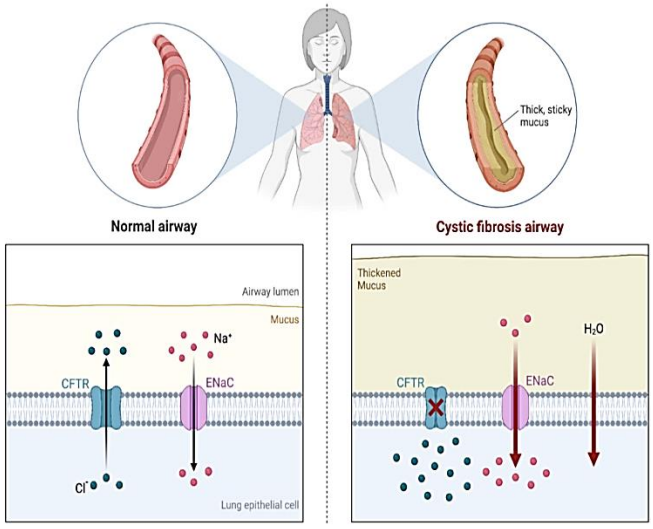


Fig. 3: Showing the Normal and cystic fibrosis airway comparison [246].

*7.4.3 Congenital Adrenal Hyperplasia (MIM: 201910)*

Congenital Adrenal Hyperplasia (CAH) is an inherited disease, and the mutation is homozygous or compound of the *CYP21A2* gene. The gene *CYP21A2* encompasses steroid 21-hydroxylase. The production of adrenal steroids is involved in facial hair growth, acne, and/or a deep voice; rapid growth of armpit and pubic hair; infertility; or reduced fertility in adolescent girls and adult women, who may also have masculine features [247, 248]. Military Hospital Rawalpindi carried out a study in 2010, and they stated that its average rate is 1:5000 in Pakistan [249]. Diagnostic tests might involve urine tests, hereditary investigations, physical checkup, family history, mutation analysis, and blood and urine testing [250, 251]. The treatment may involve glucocorticoid therapy, growth and puberty delaying agents, psychiatric advice, a combination of glucocorticoid, mineralocorticoid, aromatase inhibitors, and flutamide. Infants with uncertain genitalia are to be evaluated surgically [252, 253].

*7.4.4 Congenital Hypothyroidism (MIM: 275200).*

It is an autosomal recessively, dominantly, and X-linked inherited disorder that occurs due to a mutation in nine reported genes, i.e., *TSHR(CHNG-1), PAX8(CHNG-2), CHNG3(CHNG-3), TSHB(CHNG-4), NKX2-5(CHNG-5), THRA(CHNG-6), TRHR(CHNG-7), TBL1X(CHNG-8(X-Linked), and IRS4(CHNG-9)* [254]. Plasma TSH overload and thyroid hormone low levels are the result of resistance to thyroid-stimulating hormone (TSH) [255, 256]. There is a wide range of asymptomatic to severe hypothyroidism, no anti-thyroid antibodies, onset in infancy, as well as delayed intellectual development (when untreated), fatigue (when untreated), and constipation (when untreated) [257, 259]. Precise prevalence of congenital Hypothyroidism is not known, as no regular screening of the newborns has been carried out (Figure 4).

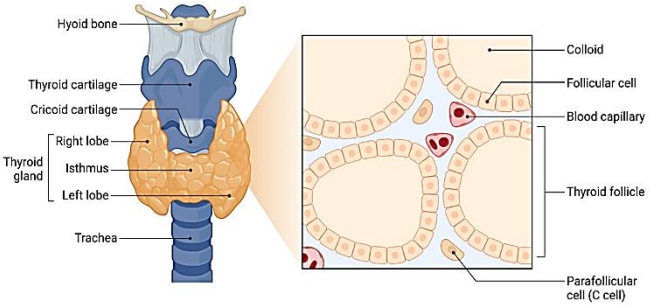


Fig. 4: Showing the thyroid gland anatomy and histology [246, 260].

It was found in Karachi hospital that the prevalence of Congenital Hypothyroidism is 1:1000 [261, 262]. Recorded that the prevalence rate of congenital hypothyroidism stood at 1:1000 newborns, which is approximately 4 times higher than that of the West, i.e., 1:4000 in the USA. Tests involve a thyroid scanning test [263, 265]. The treatment involves L-thyroxine pills, and certain nutritional supplements have been known to influence the concentration of L-thyroxine. This is in addition to fiber supplements, soy protein formulas, concentrated iron, cholestyramine and other resins, aluminum hydroxide, and sucralfate calcium [266].

7.5 Group E: Metal & Miscellaneous Disorders (2 disorders)

*7.5.1 L-2-hydroxyglutaric aciduria (L2HGA: OMIM #236792)*

L-2-hydroxyglutaric aciduria is an uncommon autosomal recessive disorder caused by pathogenic mutations in the *L2HGDH* gene [267]. The gene *L2HGDH* codes for the enzyme L-2-hydroxyglutarate dehydrogenase, which is responsible for converting L-2-hydroxyglutarate to alpha-ketoglutarate in different human tissues, in the presence of the flavin adenine dinucleotide (FAD) coenzyme. L-2-hydroxyglutaric aciduria is an extremely rare neurodegenerative metabolic disorder that is inherited in an autosomal recessive manner. The hallmark of the disease is an elevation of L-2-hydroxyglutaric acid in several body fluids, including cerebrospinal fluid, urine, and plasma [268, 269]. A range of phenotypic characteristics, including intellectual disability, developmental delays, epilepsy, behavioral issues, macrocephaly, spasticity, speech abnormalities, and cerebellar ataxia, may be present in the disease's presentations. [270, 271]. Accurate occurrence of L2HGA remains unidentified; however, there have been 93 mutations reported, and, in the Pakistani population, there have been only three mutations reported: c.1003C > T p.(Arg335*), c.180delG, p.(Ala62Profs*24), and c.178G > A p.(Gly60Arg). L2HGA can be diagnosed utilizing biochemical, radiological, and genetic testing methods [272]. Plasma amino acids and urine organic acids make up metabolic screening. The following commercial tests are available to diagnose L2HGA: EpiPanelDx PLUS genetic test, leukodystrophy and genetic geukoencephalopathy panel, nuclear mitochondrial disorders panel, comprehensive neurometabolic disorders panel, cerebral palsy spectrum disorders panel, and organic acidemias panel. The medications that may be applied to treat the disorder are Flavin adenine dinucleotide and Oxoglutaric acid [273].

*7.5.2 Wilson's Disease (MIM: 277900)*

*ATP7B* mutations cause Wilson disease (WD), an autosomal recessive copper metabolism disorder that affects biliary copper excretion and results in neurological, psychiatric, and hepatic problems [274]. Jaundice, hepatomegaly, Kayser-Fleischer rings, tremors, dystonia, and cognitive decline are among the symptoms. In Pakistan, WD is common due to consanguinity (estimated >1:30,000), with familial clusters [275]. Mutations include c.1143G>T (p.Glu381Asp); and p.His1069Gln, which is less common locally. Diagnosis uses serum CP (<20 mg/dL), 24-hour urine copper (>100 µg), liver biopsy, and *ATP7B* sequencing [276]. Treatment involves chelators (penicillamine, trientine), zinc, and liver transplant; early therapy prevents progression [277, 283].

## 8. Genetics of rare metabolic disorders in Pakistan.

Because of low prevalence, very little work has been done on genetically inherited metabolic disorders in

Pakistan. Below is the detail of inherited metabolic disorders in Pakistan (Table 4).

Summary of hallmark neurological features and primary management pillars for the 20 selected inherited metabolic disorders relevant to Pakistan are in table 6.

Table 4: Inherited Metabolic Disorders Relevant to Pakistan – Genetic, Clinical, and Management Summary.

| Category | Disorder | Gene(s) | Key Pakistani Mutations (examples) | Hallmark Neurological Features | Treatability Level | Main Management | Pakistan Notes / Prevalence | Ref |
|---|---|---|---|---|---|---|---|---|
| Group A: Amino Acid & Related Disorders | Phenylketonuria | *PAH* | c.293T>C | Severe ID, epilepsy, gait abnormalities | High | Low- Phe diet ± sapropterin | Treatable; no national NBS | [283, 286] |
| | Maple Syrup Urine Disease | *BCKDHA/B/C, DBT* | — | Lethargy, encephalopathy, maple odor | High | Branched-chain amino acid (BCAA) restriction, dialysis | Higher estimated prevalence | [284] |
| | Tyrosinemia Type I | *FAH* | c.192G>T, c.1062+5G>A | Hypotonia, developmental delay | High | Nitisinone + low-Tyr/Phe diet | Limited studies; access challenging | [282] |
| | Homocystinuria | *CBS* | p.Thr191Met | ID, seizures, psychiatric issues | High | B6, betaine, methionine (Met) restriction | High in ID cohorts (~2.1%) | [283] |
| Group B: Organic Acidurias | Methylmalonic Aciduria | *MUT* | c.689C>G | Encephalopathy, developmental delay | Mod-High | Protein restriction, carnitine, B12 | Common in consanguineous | [284] |
| | Propionic Aciduria | *PCCA/PCCB* | — | Encephalopathy, seizures | Moderate | Protein restriction, carnitine | 3–9% organic acidemias | [284] |
| | Glutaric Aciduria Type 1 | *GCDH* | c.242C>T, c.427G>A | Dystonia post-crises, macrocephaly | Mod-High | Lysine (Lys) restriction, crisis prevention | 24% in high-risk; founder effects | [284] |
| | Multiple Carboxylase Deficiency | *BTD / HLCS* | c.98_104delinsTCC, c.1612C>A | Seizures, hypotonia, alopecia | High | Biotin (5–20 mg/day) | 7–8% IMDs; biotin-responsive | [282] |
| | Isovaleric Aciduria | *IVD* | p.Arg398Gln | Sweaty feet odor, acidosis, lethargy | High | Leu restriction, glycine/carnitine | 3–4% high-risk; good prognosis | [284] |
| Group C: Lysosomal & Storage Disorders | Metachromatic Leukodystrophy | *ARSA* | c.338T>C | Progressive spasticity, ataxia, regression | Limited | Early HSCT | Rare; poor prognosis | [283] |
| | Gaucher Disease | *GBA* | c.1143G>T, c.1154G>A | Seizures, myoclonus (neuronopathic) | Moderate | ERT, substrate reduction | Underreported neuronopathic; ERT limited | [281] |
| | Niemann-Pick (esp. Type C) | *NPC1/NPC2, SMPD1* | c.1718G>C, c.1267C>T | Ataxia, dystonia, vertical gaze palsy | Moderate | Miglustat (Type C) | 5–10% LSDs; limited therapy | [283] |
| | MPS Type I | *IDUA* | c.1469T>C, c.784delC | Neurocognitive decline (severe) | Moderate | ERT (laronidase), HSCT | 83% of MPS; consanguinity high | [286] |
| | MPS Type II | *IDS* | c.353T>A | Hyperactivity, cognitive decline | Moderate | ERT (idursulfase) | 1–5% MPS; X-linked | [283] |
| Group D: Other Metabolic / Endocrine Disorders | Galactosemia | *GALT* | c.940A>G, c.563A>G | ID, speech dyspraxia, motor delay | High | Galactose-free diet | ~1:9,634; selective screening | [280, 284] |
| | Cystic Fibrosis | *CFTR* | ΔF508, c.1705T>G | Variable (mainly pulmonary) | Moderate | Antibiotics, enzymes, high-calorie diet | Increasing in consanguineous | [282] |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Congenital Adrenal Hyperplasia | *CYP21A2* | c.91C>T, c.646+1G>A | Behavioral/neurological risks if untreated | High | Glucocorticoid/mineralocorticoid | ~1:5,000 hospital-based | — |
| | Congenital Hypothyroidism | *TSHR, PAX8, others* | c.1349G>A, c.1657G>A | ID, developmental delay (untreated) | High | Levothyroxine | ~1:1,000 (4× global) | — |
| Group E: Metal & Miscellaneous Disorders | L-2-Hydroxyglutaric Aciduria | *L2HGDH* | c.1003C>T, c.180delG | ID, ataxia, macrocephaly | Limited | Supportive; riboflavin trials | Novel mutations in Pakistani families | [282, 284] |
| | Wilson Disease | *ATP7B* | c.1143G>T | Tremors, dystonia, psychiatric | High | Chelators, zinc | >1:30,000; familial clusters | — |

Table 5 provides a comparative overview of the treatability profiles for the 20 selected inherited metabolic disorders, emphasizing key therapeutic interventions, their potential to prevent or mitigate irreversible neurological damage, and relevant evidence from Pakistani cohorts in the context of high consanguinity and limited newborn screening infrastructure.

Table 5: Comparative overview of treatability, key interventions, neurological protection potential, and Pakistan-specific evidence for selected inherited metabolic disorders.

| Disorder | Treatability | Key Intervention(s) | Neuroprotection Potential | Pakistan Evidence / Notes |
|---|---|---|---|---|
| Galactosemia | High | Galactose-free diet | High | ~1:9,634; prevents severe ID |
| Phenylketonuria | High | Low-Phe diet ± sapropterin | Very High | Treatable; irreversible if late |
| Congenital Hypothyroidism | High | Levothyroxine | Very High | ~1:1,000; fully preventable |
| Multiple Carboxylase Deficiency | High | Biotin 5–20 mg/day | Very High | 7–8% IMDs; rapid response |
| Homocystinuria | High | B6, betaine, Met restriction | High | ~2.1% ID cohorts |
| Isovaleric Aciduria | High | Leu restriction, glycine/carnitine | High | Good prognosis early |
| Maple Syrup Urine Disease | High | Branched-chain amino acid (BCAA) restriction, dialysis | Very High | Urgent treatment critical |
| Wilson Disease | High | Chelators, zinc | High | >1:30,000; early prevents progression |
| Tyrosinemia Type I | High | Nitisinone + diet | High | Transformative if accessible |
| Congenital Adrenal Hyperplasia | High | Glucocorticoid/mineralocorticoid | High | ~1:5,000; lifelong therapy |
| Glutaric Aciduria Type 1 | Mod-High | Lysine restriction, crisis prevention | High | 24% high-risk; presymptomatic key |
| Methylmalonic Aciduria | Mod-High | Protein restriction, carnitine/B12 | Mod-High | Common consanguineous |
| Propionic Aciduria | Moderate | Protein restriction, carnitine | Moderate | 3–9% organic acidemias |
| MPS Type I | Moderate | ERT, HSCT (early) | Mod-High | 83% MPS; early halts progression |
| MPS Type II | Moderate | ERT | Moderate | X-linked; slower neuro benefit |
| Gaucher (Type I) | Moderate | ERT, substrate reduction | Moderate | ERT limited; neuronopathic underreported |
| Niemann-Pick (Type C) | Moderate | Miglustat | Moderate | 5–10% LSDs; stabilizes neurology |
| Cystic Fibrosis | Moderate | Antibiotics, enzymes, diet | Moderate | Mainly pulmonary; variable neuro |
| Metachromatic Leukodystrophy | Limited | Early HSCT | Low-Mod | Poor prognosis late |
| L-2-Hydroxyglutaric Aciduria | Limited | Supportive; riboflavin trials | Low | Novel local mutations; supportive only |

Table 6. Consolidated summary of hallmark neurological features and primary management pillars for the 20 selected inherited metabolic disorders relevant to Pakistan.

| Disorder | Hallmark Neurological Features | Primary Management Pillars | Treatability Level | Key Notes (Pakistan Context) |
|---|---|---|---|---|
| Galactosemia | Intellectual disability, speech dyspraxia, motor dysfunction, developmental delay | Lifelong galactose/lactose-free diet | High | ~1:9,634 reported; early diet prevents severe outcomes |
| Phenylketonuria (PKU) | Severe intellectual disability, epilepsy, gait abnormalities, regression | Low-Phe diet ± sapropterin (tetrahydrobiopterin ($BH_4$)) | High | Treatable but irreversible damage if late; no national NBS |
| Maple Syrup Urine Disease (MSUD) | Encephalopathy, seizures, lethargy, developmental | Branched-chain amino acid (BCAA) restriction, dialysis | High | Higher estimated prevalence; urgent treatment critical |

| | | | | |
|---|---|---|---|---|
| | delay | in crises | | |
| Homocystinuria | Intellectual disability, seizures, psychiatric disturbances | Pyridoxine (B6), betaine, Met-restricted diet | High | ~2.1% in intellectual disability cohorts; consanguinity |
| Congenital Hypothyroidism | Intellectual disability, developmental delay, hypotonia (untreated) | Lifelong levothyroxine | High | ~1:1,000 (4× global rate); fully preventable if early |
| Multiple Carboxylase Deficiency | Seizures, hypotonia, developmental delay, alopecia | Oral biotin (5–20 mg/day) | High | 7–8% of IMDs in registries; rapid response to biotin |
| Isovaleric Aciduria | Lethargy, seizures, developmental delay, "sweaty feet" odor | Leu restriction, glycine/carnitine supplementation | High | 3–4% in high-risk screening; excellent prognosis if early |
| Wilson Disease | Tremors, dystonia, psychiatric symptoms, cognitive decline | Chelators (penicillamine/trientine), zinc, transplant | High | >1:30,000 due to consanguinity; early therapy key |
| Tyrosinemia Type I | Hypotonia, developmental delay (secondary to liver/renal) | Nitisinone + low- Tyr/Phe diet | High | Limited studies; nitisinone access remains challenging |
| Congenital Adrenal Hyperplasia | Behavioral/neurological risks if untreated crises | Glucocorticoid + mineralocorticoid replacement | High | ~1:5,000 hospital-based; lifelong therapy required |
| Glutaric Aciduria Type 1 | Dystonia (post-encephalopathic crises), macrocephaly | Lysine/tryptophan restriction, carnitine, crisis prevention | Mod-High | 24% in high-risk screening; founder effects |
| Methylmalonic Aciduria | Encephalopathy, developmental delay, seizures | Protein restriction, carnitine, vitamin B12 (responsive), transplant | Mod-High | Common in consanguineous families |
| Propionic Aciduria | Encephalopathy, seizures, hypotonia | Protein restriction, carnitine, metronidazole | Moderate | 3–9% of organic acidemias in hospital cohorts |
| Mucopolysaccharidosis Type I (MPS I) | Neurocognitive decline (severe Hurler form) | Enzyme replacement (laronidase), early HSCT | Moderate | 83% of MPS cases; early intervention halts progression |
| Mucopolysaccharidosis Type II (MPS II) | Hyperactivity, cognitive decline, seizures | Enzyme replacement (idursulfase) | Moderate | 1–5% of MPS; X-linked; consanguineous reports |
| Gaucher Disease (esp. neuronopathic) | Seizures, myoclonus, gaze palsy (Type III) | Enzyme replacement therapy, substrate reduction | Moderate | Neuronopathic forms underreported; ERT access limited |
| Niemann-Pick Disease (esp. Type C) | Ataxia, dystonia, vertical supranuclear gaze palsy | Miglustat (Type C), supportive care | Moderate | 5–10% of lysosomal disorders; limited therapy access |
| Cystic Fibrosis | Variable (mainly pulmonary; occasional hypotonia) | Antibiotics, mucolytics, pancreatic enzymes, high-calorie diet | Moderate | Increasing recognition in consanguineous families |
| Metachromatic Leukodystrophy | Progressive spasticity, ataxia, regression, seizures | Early hematopoietic stem cell transplantation | Limited | Rare; poor prognosis without very early intervention |
| L-2-Hydroxyglutaric Aciduria | Intellectual disability, cerebellar ataxia, macrocephaly | Supportive care; riboflavin/FAD trials (experimental) | Limited | Novel truncating mutations reported in Pakistani families |

## 9. Conclusions

Inherited metabolic disorders are rare recessive disorders that are characterized by variable phenotypes, including mild to severe intellectual Disability (ID). The scientific literature has so far reported more than 1500 different inherited metabolic disorders. However, in Pakistan, only a few are known, and among those causative genes and their mutations are still unknown in many cases. Based on the literature, follow-up studies are needed to identify the genetic basis of these rare disorders in the neonatal period to mitigate their adverse effects.

*Establishment of a Centralized Patient Registry*

Create a national IMD registry under the Pakistan Health Research Council or the Ministry of Health, with secure, web-based data entry from tertiary centers. Include phenotypic, biochemical, genetic, and outcome data to track prevalence, founder mutations, and treatment responses in consanguineous cohorts. Mandate reporting from provincial metabolic units; integrate with existing rare disease efforts for epidemiological insights and policy advocacy.

*Strategies to Improve Access to Orphan Drugs and Specialized Nutrition:*

Develop an orphan drug policy with tax incentives, expedited registration, and public-private partnerships for import/manufacture of essential therapies (e.g., sapropterin, nitisinone, biotin, special formulas). Subsidize food for special medical purposes (FSMP) via provincial health budgets or insurance schemes; establish centralized

procurement/distribution hubs in major cities to reduce costs and ensure equitable access, especially for treatable conditions like PKU and organic acidurias.

*Integration of Genetic Counseling into Primary Care:*

Train primary care physicians (via short CME modules) and nurses in basic genetic risk assessment and referral pathways. Establish a national genetic counseling training program (e.g., 2-year Master's at institutions like AKU or Gomal University) to produce 50–100 counselors over 5 years. Integrate counseling into antenatal clinics, thalassemia carrier programs, and consanguinity-aware family planning services; partner with religious/community leaders for culturally sensitive education on carrier screening and prenatal diagnosis.

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**Authors Contribution**

M.M. conceptualized the study, developed the methodology, provided supervision, prepared the original draft, and contributed to writing – review & editing. M.S performed the investigation, handled data curation, and participated in writing – review & editing. A.S.K conducted formal analysis. S.I. carried out the investigation and provided resources. A.Si. contributed to the investigation. H.M. was involved in the investigation and prepared visualizations. S.B performed validation. A.Sa. and M.H handled data curation. K.N.H. contributed to writing, review & editing. S.A.R. was responsible for the software and took part in the investigation. H.B.H. participated in the investigation and contributed to writing, review & editing. H.G. provided resources and performed validation. J.K. was involved in the investigation and contributed to writing, review & editing. M.A.K and S.A. helped with conceptualization and writing – review & editing. All authors read and approved the final version of the manuscript.

**Conflict of interest**

None asserted by authors

**Data Availability Statement**

Data will be available on request by the corresponding authors.

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