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# Ribose-5-Phosphate Isomerase Deficiency: Exploring One of the World's Rarest Pediatric Metabolic Disorders

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**Executive Summary**

Ribose-5-Phosphate Isomerase (RPI) Deficiency is an exceptionally rare autosomal recessive disorder caused by mutations in the RPIA gene. With only five known cases worldwide as of 2025, it is among the rarest human diseases. The disorder impairs the non-oxidative phase of the pentose phosphate pathway, leading to toxic accumulation of polyols (D-ribitol and D-arabitol) that cause progressive leukoencephalopathy and severe neurological damage.

Affected individuals typically develop psychomotor delay, epilepsy, ataxia, spasticity, optic atrophy, and intellectual disability in early childhood, while visceral organs are usually spared. Diagnosis integrates clinical findings, brain MRI and magnetic resonance spectroscopy (MRS), detection of elevated polyols in body fluids, and genetic confirmation. Management is supportive, with no curative treatment currently available.

This review provides a comprehensive overview of the biochemistry, genetics, clinical presentation, diagnostic challenges, and future therapeutic prospects for RPI deficiency. It highlights the unique insights this ultra-rare condition offers into brain metabolism and underscores the importance of international collaboration in advancing research and care for rare pediatric diseases.

**Abstract:**

Ribose-5-Phosphate Isomerase (RPI) Deficiency is an exceptionally rare autosomal recessive genetic disorder caused by mutations in the RPIA gene (Gard, 2026). With only five known cases documented worldwide as of 2025, it is considered one of the rarest human diseases. The disorder impairs the pentose phosphate pathway, resulting in the toxic accumulation of polyols that cause progressive white matter damage in the brain(Huck et al., 2004). Affected children typically experience developmental delay, epilepsy, neurological regression, ataxia, spasticity, optic atrophy, and leukoencephalopathy (Knaap et al., 1999). This review synthesizes current knowledge on the biochemistry, clinical presentation, diagnostic challenges, and prospects of RPI deficiency, highlighting broader implications for rare disease research in pediatrics.

## 1. Introduction:

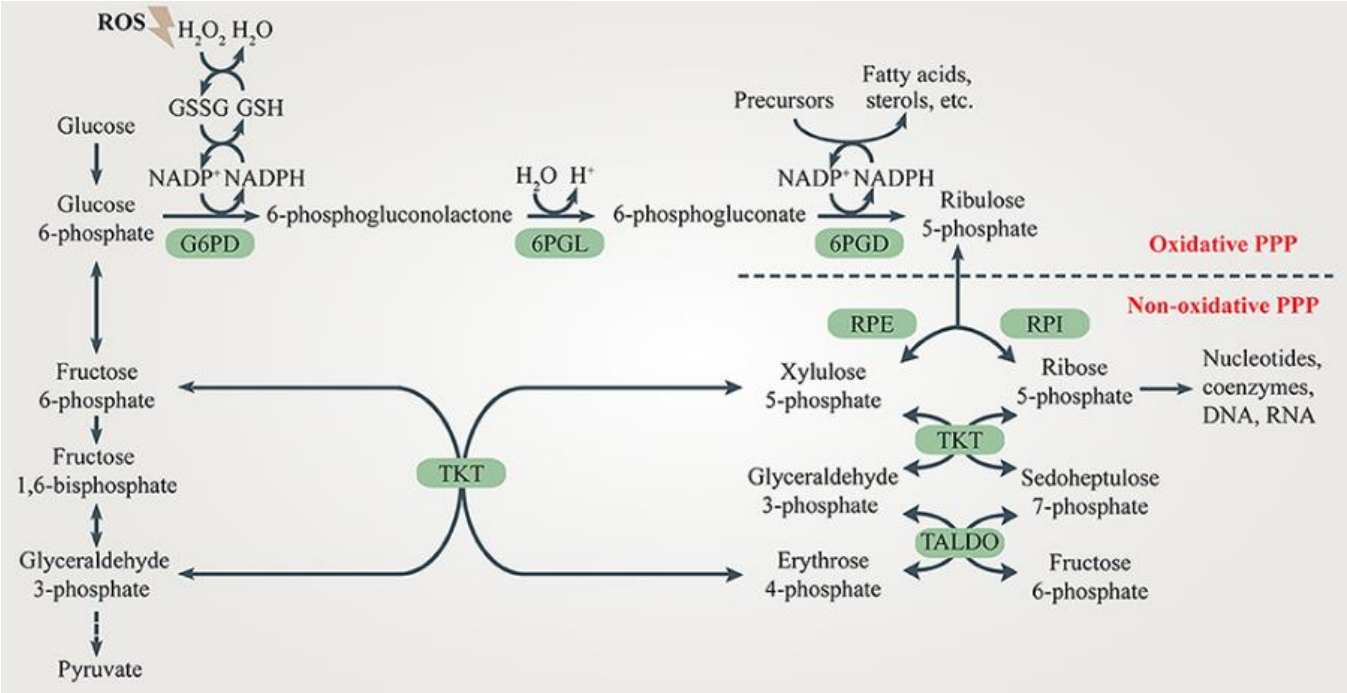
In the vast landscape of human medicine, certain conditions remain so rare that they challenge our understanding of biology and expose gaps in healthcare systems. Ribose-5-Phosphate Isomerase Deficiency (RPI deficiency or RPID) is one such disorder. First formally described in 1999, it is frequently

regarded as the second-rarest human disease, with only five known cases identified to date. This progressive metabolic disorder primarily affects the central nervous system of children, leading to severe neurological impairment despite sparing other major organs. The condition offers a unique window into the intricate relationship between cellular metabolism and brain development. This article explores the underlying science, real-world clinical impact, and future possibilities for RPI deficiency, aiming to raise awareness of ultra-rare pediatric diseases.

## 2. Biochemistry and Genetics:

The pentose phosphate pathway (PPP) is a critical metabolic network that branches from glycolysis at glucose-6-phosphate. It serves two main functions: (1) generating NADPH, a key reducing agent for biosynthetic reactions and cellular antioxidant defense against oxidative stress (particularly vital for neurons with high metabolic demands), and (2) producing ribose-5-phosphate, an essential precursor for nucleotide synthesis in rapidly dividing cells. The pathway consists of an irreversible oxidative phase and a reversible non-oxidative phase, the latter allowing interconversion of sugars for flexible metabolic adaptation.

**Figure 1: Simplified Pentose Phosphate Pathway**




Ribose-5-Phosphate Isomerase (RPI), encoded by the RPIA gene on chromosome 2p11.2, catalyzes the reversible isomerization of ribulose-5-phosphate to ribose-5-phosphate in the non-oxidative phase(Kalyani et al., 2025). Pathogenic mutations in RPIA are typically loss-of-function variants such as frameshifts, missense changes (e.g., p.A61V), or others that severely impair this activity(Wamelink et al., 2010). This blockage diverts upstream metabolites toward alternative pathways, resulting in the accumulation of pentoses and their reduction to polyols like D-ribitol and D-arabitol. These polyols build up in brain tissue, cerebrospinal fluid, plasma, and urine, exerting presumed toxic effects through osmotic stress, oxidative damage, or direct interference with cellular processes, ultimately driving leukoencephalopathy and neuronal dysfunction. The disorder follows an autosomal recessive inheritance

pattern, with affected individuals harboring homozygous or compound heterozygous RPIA variants. Carrier frequency is unknown due to extreme rarity, but consanguinity or founder effects may play a role in reported cases.

### 3. Clinical Presentation and Known Cases:

Symptoms of RPI deficiency generally emerge in infancy or early childhood and follow a slowly progressive course, though onset and severity can vary. Core manifestations include psychomotor developmental delay, epilepsy (often starting in early childhood), cerebellar ataxia, spasticity, optic atrophy, sensorimotor neuropathy, and extensive white matter abnormalities visible on MRI as leukoencephalopathy(Kalyani et al., 2025). Additional features may include dysarthria, movement disorders (e.g., athetoid movements), hypotonia (especially in neonatal-onset cases), and intellectual disability. Notably, there is typically no organomegaly or major dysfunction of visceral organs, distinguishing it from some other storage disorders.

**Figure 2: Representative Brain MRI Findings**

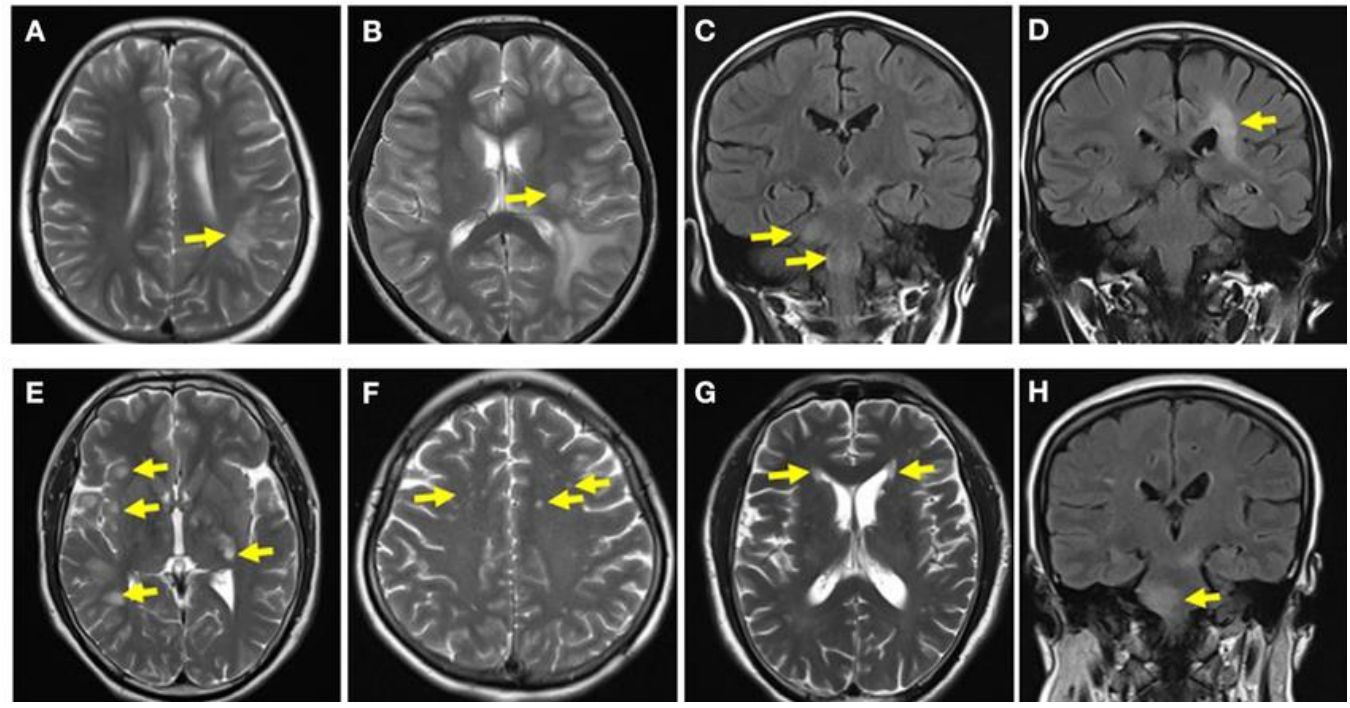



**Table 1: Summary of Reported Cases of RPI Deficiency**

| | Case | Year | Patient Profile | Major Clinical Features Key Diagnostic Findings |
|---|---|---|---|---|
| Features Key | 1999/2004 | Dutch male, born 1984 | Psychomotor delay from early life, epilepsy (onset approximately age 4), progressive regression from age 7 with prominent cerebellar ataxia, mild spasticity, | Elevated polyols (ribitol, D-arabitol) in brain (MRS), plasma, urine, CSF, leukoencephalopathy on MRI, deficient RPI activity in fibroblasts, compound heterozygous RPIA |

| | | | | |
|---|---|---|---|---|
| | | | optic atrophy, mild sensorimotor neuropathy | mutations (frameshift + missense)(Kalyani et al., 2025) |
| 2 | 2017 | 18-year-old male (Indian origin) | Seizures, psychomotor regression, diffuse white matter changes | Elevated polyols, MRI abnormalities, and genetic confirmation(Naik et al., 2017) |
| changes Elevateds Elevated | Young child with neonatal onset | Neonatal hypotonia, severe psychomotor delay, leukoencephalopathy | Whole-exome sequencing identified RPIA mutations, MRI and biochemical findings(Brooks et al., 2018) | |
| onset Neonatalt. Neonatal9 | Young child | Progressive neurological decline, leukoencephalopathy, peripheral neuropathy | Elevated urinary polyols (arabitol, ribitol), RPIA variants confirmed(Kalyani et al., 2025) | |
| neuropathy Elevated5 | Childhood-onset (adult presentation noted in abstract). | Epilepsy (e.g., juvenile myoclonic), learning disability, possible gout history in one report | Confirmed via genetic testing; highlights diagnostic complexity(Kalyani et al., 2025) | |

**report. Confirmed. Confirmed. Summaries are synthesized from primary reports; exact details may vary slightly by source. The fifth case underscores ongoing challenges in adult or atypical presentations.**

## 4. Diagnosis and Challenges:

Definitive diagnosis integrates clinical suspicion, neuroimaging, biochemical testing, and molecular confirmation. Brain proton magnetic resonance spectroscopy (MRS) often reveals strikingly elevated polyol peaks, and elevated D-ribitol and D-arabitol are detectable in body fluids (urine, plasma, CSF) via specialized assays (e.g., gas chromatography–mass spectrometry); enzyme activity can be measured in fibroblasts, though genetic testing (targeted RPIA sequencing or whole-exome/genome sequencing) is now the gold standard(Kalyani et al., 2025).

Significant challenges arise from symptom overlap with cerebral palsy, mitochondrial disorders, other leukodystrophies (e.g., vanishing white matter disease), and peroxisomal disorders. This frequently results in prolonged diagnostic odysseys spanning years. RPI deficiency is not included in standard newborn screening panels(Kalyani et al., 2025), and awareness among clinicians remains low due to its rarity. Early consideration in unexplained progressive leukoencephalopathy with polyol accumulation is key.

## 5. Treatment and Management:

No curative treatment currently exists(Kalyani et al., 2025). Management is supportive and multidisciplinary, involving pediatric neurologists, geneticists, metabolic specialists, physical and occupational therapists, ophthalmologists, and epileptologists. Interventions include anti-seizure medications tailored to epilepsy type, physical therapy to address spasticity and ataxia, nutritional support, and monitoring for complications like vision loss. Regular neuroimaging and developmental assessments guide care. Emerging research explores targeted approaches, such as gene therapy to restore RPIA function, small molecules to mitigate polyol accumulation or enhance alternative metabolic routes, and antioxidant strategies to counter oxidative stress. Insights from related PPP disorders (e.g., transaldolase deficiency) may inform future therapies. International registries and collaborative networks are essential for advancing natural history studies and clinical trials in such ultra-rare conditions.

## 6. Conclusion:

Ribose-5-Phosphate Isomerase Deficiency, though affecting an extraordinarily small number of individuals, carries outsized scientific and humanitarian significance. It exemplifies how a defect in a single enzyme can profoundly disrupt brain function and highlights the immense difficulties families and clinicians face when confronting ultra-rare conditions.

As genetic testing becomes more accessible and international collaboration strengthens, there is renewed hope for earlier diagnosis and potential targeted therapies. Ultimately, the story of RPI deficiency reminds us that every rare disease represents real children and families deserving of attention, compassion, and continued scientific pursuit. Advancing research in this area not only benefits those directly affected but also deepens our collective understanding of human metabolism and neurological health.

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