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Review article

Disorders of purine biosynthesis metabolism

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ABSTRACT

Purines are essential molecules that are components of vital biomolecules, such as nucleic acids, coenzymes, signaling molecules, as well as energy transfer molecules. The *de novo* biosynthesis pathway starts from phosphoribosylpyrophosphate (PRPP) and eventually leads to the synthesis of inosine monophosphate (IMP) by means of 10 sequential steps catalyzed by six different enzymes, three of which are bi-or tri-functional in nature. IMP is then converted into guanosine monophosphate (GMP) or adenosine monophosphate (AMP), which are further phosphorylated into nucleoside di- or tri-phosphates, such as GDP, GTP, ADP and ATP. This review provides an overview of inborn errors of metabolism pertaining to purine synthesis in humans, including either phosphoribosylpyrophosphate synthetase (PRS) overactivity or deficiency, as well as adenylosuccinate lyase (ADSL), 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (ATIC), phosphoribosylaminoimidazole succinocarboxamide synthetase (PAICS), and adenylosuccinate synthetase (ADSS) deficiencies. ITPase deficiency is being described as well. The clinical spectrum of these disorders is broad, including neurological impairment, such as psychomotor retardation, epilepsy, hypotonia, or microcephaly; sensory involvement, such as deafness and visual disturbances; multiple malformations, as well as muscle presentations or consequences of hyperuricemia, such as gouty arthritis or kidney stones. Clinical signs are often nonspecific and, thus, overlooked. It is to be hoped that this is likely to be gradually overcome by using sensitive biochemical investigations and next-generation sequencing technologies.

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1. Introduction

Purines are essential cellular components that are incorporated into nucleic acids, coenzymes (*i.e.* Coenzyme A, FAD, NAD, NADP, adenosylcobalamin), signaling molecules (cAMP and cGMP) and energy

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transfer molecules (ATP and GTP). Purine metabolism is divided into three pathways: the *de novo* biosynthetic pathway (Fig. 1 in blue), which generates inosine monophosphate (IMP); the catabolic pathway, which generates uric acid; and the salvage pathway, which reconverts guanine, hypoxanthine, and adenine into GMP, IMP, and AMP, respectively. The key precursor for *de novo* purine biosynthesis is phosphoribosylpyrophosphate (PRPP), which is synthesized by PRPP synthetase (PRS), a highly regulated enzyme that uses ribose-5-phosphate from the pentose phosphate pathway and ATP as substrates (Fig. 1). Three PRS genes have been identified, a single one of which is X-linked (*PRPS1*); this gene has been associated with two human diseases, consisting of PRS overactivity and PRS deficiency [1]. The *de novo* purine biosynthesis refers to the assembling of a purine base onto a PRPP backbone following 10 sequential enzymatic reactions that are catalyzed by six enzymes (PPAT, GART, PFAS, PAICS, ADSL and ATIC), interacting inside the cells in multi-enzyme complexes called purinosomes [2] (see Fig. 1 and legend for full names of the enzymes).

To date, inborn errors of metabolism on account of three enzyme deficiencies of the *de novo* purine biosynthesis have been reported in humans, including PAICS, ADSL, and ATIC. IMP, which is the final product of *de novo* purine biosynthesis, is then converted into AMP or GMP. AMP synthesis is catalyzed by adenylosuccinate synthase (ADSS) and ADSL. GMP synthesis is catalyzed by IMP dehydrogenase (IMPDH), which is then followed by GMP synthase (GMPS) (Fig. 1). Muscular ADSS deficiency has recently been described as being a causal factor of myopathy, which is apparently more common in Asian populations [3].

This review is focused on the description of the two PRS-1-related disorders, the three reported *de novo* purine biosynthesis genetic diseases (PAICS, ADSL, and ATIC deficiencies), muscular ADSS deficiency, as well as ITPase deficiency. This latter enzyme removes non-canonical (deoxy-)ITP and (deoxy-)XTP nucleotides so as to prevent their toxic incorporation into nucleic acids [4,5]. These seven disorders constitute heterogeneous phenotypes that are characterized by a spectrum of malformations, neurological impairments, and uric acid

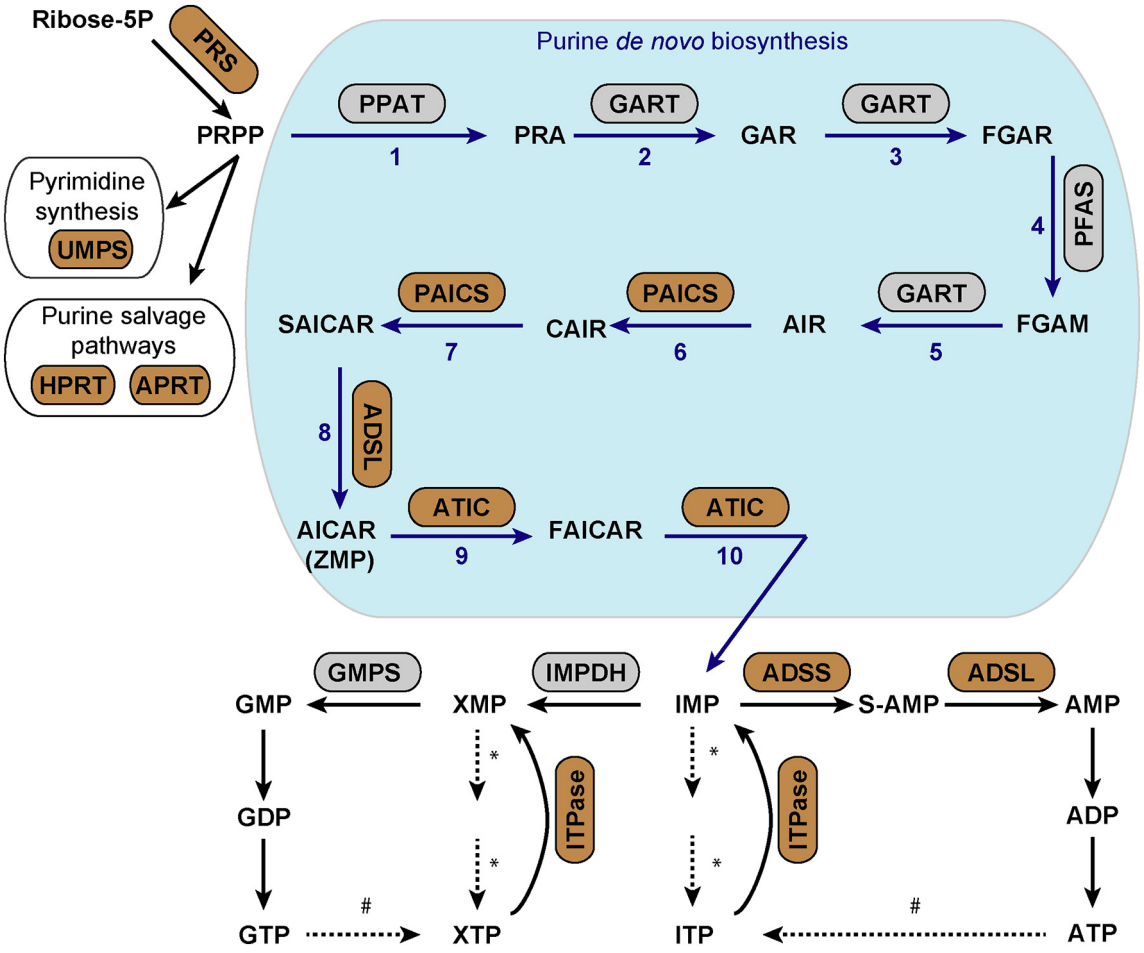

Fig. 1. Purine nucleotide synthesis.
PRPP synthesis is catalyzed by PRS. PRPP is the key precursor of purine biosynthesis. Yet, it is also involved in purine salvage pathways and pyrimidine synthesis. The 10 steps of purine *de novo* biosynthesis, highlighted in light blue, from PRPP toward IMP are represented by blue arrows and numbers. AMP and GMP synthesis are catalyzed by two sequential enzymatic reactions from IMP. These mononucleotides are then phosphorylated into their respective nucleoside di- and tri-phosphates GDP, GTP, ADP and ATP, respectively. XTP and ITP are byproducts resulting from either phosphorylations (*) or deaminations (#), which are degraded by ITPase. The enzymes are represented in grey or brown boxes. The reported human deficiencies are highlighted in brown. PRPP, phosphoribosylpyrophosphate; PRA, 5-phosphoribosylamine; GAR, glycinamide ribonucleotide; FGAR, formylglycinamide ribonucleotide; FGAM, formylglicinamidine ribonucleotide; AIR, aminoimidazole ribonucleotide; CAIR, 4-carboxy-5-aminoimidazole ribonucleotide; SAICAR, 4-(N-succinylcarboxamide)-5-aminoimidazole ribonucleotide; AICAR, aminoimidazole-4-carboxamide ribonucleotide; FAICAR, formylaminoimidazole-4-carboxamide ribonucleotide; IMP, inosine 5′ monophosphate; ITP, inosine 5′ triphosphate; S-AMP, succinyl-adenosine 5′ monophosphate (adenylosuccinate); ADP, adenosine 5′ diphosphate; ATP, adenosine 5′ triphosphate; XMP, xanthosine 5′ monophosphate; XTP, xanthosine 5′ triphosphate; GMP, guanosine 5′ monophosphate; GDP, guanosine 5′ diphosphate; GTP, guanosine 5′ triphosphate. PRS, PRPP synthetase; UMPS, uridine monophosphate synthase; HPRT, hypoxanthine-guanine phosphoribosyltransferase; APRT, adenine phosphoribosyltransferase; PPAT, PRPP amidotransferase; GART, trifunctional purine biosynthetic protein: glycinamide ribonucleotide synthase/glycinamide ribonucleotide transformylase/aminoimidazole ribonucleotide synthase; PFAS, phosphoribosyl-formylglycinamidine synthase; PAICS, bifunctional phosphoribosyl-aminoimidazole carboxylase/phosphoribosyl-aminoimidazole succinocarboxamide synthetase ADSL, adenylosuccinate lyase; ATIC, AICAR transformylase/IMP cyclohydrolase; IMPDH, IMP dehydrogenase; GMPS, GMP synthase; ADSS, adenylosuccinate synthase.

Table 1
Summary of purine biosynthesis disorders and related diseases.

Disorder / enzyme defect Gene - Inheritance	Phenotypes & OMIM number	Number of patients/families reported	Clinical features	Biochemical testing	Imaging and/or biopsy	References
Phosphoribosylpyrophosphate synthetase (PRS) overactivity *PRPS1* XL	PRPP synthetase superactivity due to gain-of-function variants: early-onset phenotype (OMIM 300661) Gout, PRS-related, milder phenotype (OMIM 300661)	<10 families with gain-of-function pathogenic variant > 20 families with PRS-related hyperuricemia	Nephrolithiasis, gout and progressive renal failure Early onset phenotype: +/− deafness, hypotonia, developmental delay, ataxia, short stature, recurrent respiratory infections, facial dysmorphia	↑ Uric acid (U, P); ↑ Hypoxanthine (U) ↑ PRPP and nucleotides (RBC, F, L) ↑ PRS activity or lack of allosteric regulation (RBC*, F, L) ↑ *PRPS1* transcript (by qPCR) and ↑ PRS-I isoform (by western blot or IF)		[1,7,8,9,10,11,13 14,15,16,17,18]
Phosphoribosylpyrophosphate synthetase (PRS) deficiency *PRPS1* XL	Arts syndrome (OMIM #301835) Charcot-Marie-Tooth disease-5 CMTX5 (OMIM #311070) X-linked non-syndromic hearing loss DFNX1 (OMIM #304500)	~ 30–40 patients	Sensorineural deafness +/− Developmental delay +/− Ataxia +/− Peripheral neuropathy +/− Optic atrophy +/− Intellectual disability +/− Recurent respiratory infections	↓ PRS activity (RBC, F, L) n↓Hypoxanthine; n↑ orotic acid (U) n↓ uric acid (P) ↓ ATP, GTP, NAD and NADP (RBC)	Brain MRI: mild parietal and cerebellar atrophy. Brain MRI in severe phenotype: thin corpus callosum with a tapered splenium and lack of isthmus. Prominence of the anterior extra axial fluid spaces diminished over time.	[1,10,20,21,22,23,24,25,26,27,28]
Bifunctional enzyme phosphoribosylaminoimidazole carboxylase/phosphoribosylaminoimidazole succinocarboxamide synthetase (PAICS) deficiency *PAICS* AR	Not available	2 patients from 1 family	Polyhydramnios and intrauteine growth retardation Multiple malformation: skeletal, facial dysmorphia, choanal atresia, pulmonary hypoplasia, esophagus atresia, genitourinary abnormalities	↑(?) AI-riboside in body fluids	Severe malformations	[31,32]
Adenylosuccinate lyase (ADSL) deficiency *ADSL* AR	Adenylosuccinase deficiency (OMIM #103050)	> 120 patients	Developmental delay Epilepsy Autism, steroetypies, ataxia	↑ S-Adenosine (U, CSF) ↑ SAICA-riboside (U, CSF) S-Ado/SAICAr ratio correlates with severity	Brain MRI: unspecific findings with atrophy of the cerebral cortex, corpus callosum, cerebellar vermis, and anomalies of the white matter like delayed or lack of myelination	[33,35,36,37]
AICAR transformylase/IMP cyclohydrolase (ATIC) deficiency *ATIC* AR	AICA-ribosiduria (OMIM #608688)	5 patients from 4 families	Intrauteine growth retardation Severe psychomotor retardation Chorioretinal atrophy Severe scoliosis Facial dysmorphia +/−Epilepsy +/− cardiovascular defects	↑↑ AICA-riboside (U) ↑ S-Adenosine (U) n↑ SAICA-riboside (U)	Normal brain MRI and unusual morphology of the bulb, signal abnormality of the dorsal nuclei of the brainstem, thick corpus callosum, delayed myelination in one patient	[39,40]
Adenylosuccinate synthase (ADSS) muscular isoform deficiency *ADSSL1* AR	Distal myopathy-5 (MPD5) (OMIM #617030)	> 70 families	Distal myopathy predominantly but also possible in proximal and listal leg muscles +/− respiratory failure +/− dysphagia due to masticatory dyfunction +/− left ventricule hypertrophy Fetal akinesia	mild ↑ CK	Muscular histology findings: Nemaline bodies, increased lipid droplets, myofibrillar disorganization Muscle MRI of tongue and masseter muscle: diffuse fatty infiltration	[41,43,44]

(continued on next page)

Table 1 (*continued*)

Disorder / enzyme defect Gene - Inheritance	Phenotypes & OMIM number	Number of patients/families reported	Clinical features	Biochemical testing	Imaging and/or biopsy	References
Inosine triphosphatase deficiency *ITPA* AR	ITPase encephalopathy Epileptic encephaloptahy, early infantile 35 (EIEE35) (OMIM #616647)	10 patients from 7 families	Infantile encephalopathy Progressive microcephaly Severe developmental delay Epilepsy +/− Bilateral cataract +/− Cardiomyopathy	↑ ITP and IDP (RBC**) ↓ ITPase activity (RBC**, fibroblasts)	Distinct brain MRI pattern characterized by a high T2 signal and restricted diffusion in the posterior limb of the internal capsule in combination with delayed myelination and progressive cerebral atrophy. More variable are T2 signal abnormalities and diffusion restriction in the optic radiation, mesencephalic pyramidal tracts or entire cerebral peduncles, hilum of the dentate nucleus, cerebellar peduncles, and cerebellar white matter.	[45,46,47,50,51,52]

XL, X-linked; AR autosomic recessive; RBC, red blood cells; U, urine; P, plasma; F, fibroblasts; L, lymphoblasts; IF, isoelectrofocusing electrophoresis; n↑ refers to normal or slightly elevated values.

* In contrast, PRS activity in RBC is decreased in PRS synthetase superactivity linked to gain-of-function variants, probably because of enzyme lability in post-mitotic cells.

** ITP levels and ITPase activity in RBC do not permit to discriminate between ITPase encephalopathy or the presence of *ITPA* variants of pharmacogenetics relevance.

overproduction symptoms [6]. Except for PRS-related disorders that are X-linked, the diseases herein described are all autosomal recessive inherited metabolic diseases. For each disorder, a summary of the gene involved, estimated number of reported patients, clinical signs, and suggestive biochemical tests are described in detail in Table 1. Although these metabolic hereditary diseases are extremely rare, they are most probably under-diagnosed. When confronted with suggestive clinical or laboratory signs, clinicians should prescribe a dedicated biochemical screening in association with next-generation sequencing tests, which is most likely to increase the number of patients reported in the literature.

2. Phosphoribosylpyrophosphate synthetase (PRS) overactivity

PRS overactivity, which was first reported in the 1970's [7], may be caused by two different mechanisms, comprising either the presence of gain-of-function missense mutations affecting enzyme regulations (known as "PRS superactivity") [1,8] or an accelerated *PRPS1* transcription, for which no genetic defect has so far been identified (known as "PRS-related hyperuricemia") [1,9,10]. Due to an increased production of PRPP, patients affected by PRS-overactivity generate a higher synthesis of purines, thereby resulting in an increased uric acid production. The reason for this is that, while being the first rate-limiting enzyme of the *de novo* purine biosynthesis, PPAT is not saturated by PRPP (Fig. 1). Uric acid overproduction is typical to this disease, mainly resulting in uric acid lithiasis and gouty arthritis [1,11]. Remarkably, the increased PRPP availability and therefore of the *de novo* biosynthesis flux and uric acid overproduction is also observed in hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency in the purine salvage pathway (Fig. 1). In that deficiency, this is due to a co-substrate accumulation (PRPP) combined to the lower production of GMP and IMP (the HPRT products), which are inhibitors of PPAT [12]. Two clinical phenotypes have been described, comprising a severe phenotype with early-childhood-onset, as well as a milder form with adolescence- or early-adulthood-onset. The severe phenotype ("PRS-superactivity"), which is less common than the milder phenotype, associates a variable combination of clinical signs that are commonly observed in PRS deficiency (see next section), including sensorineural deafness, hypotonia, developmental delay, short stature, ataxia, recurrent respiratory infections, as well as facial dysmorphia [11,13,14]. Laboratory testing relies on hyperuricemia, uric acid urolithiasis, uric acid crystalluria, high urinary uric acid, and hypoxanthine excretion, the latter being best assessed *via* 24-hour urine samplings. A high PRS activity or lack of allosteric regulation in cells, such as fibroblasts, lymphoblasts, or red blood cells, confirms the diagnosis in all phenotypes. Considering the milder phenotype, *PRPS1* transcript using qPCR amplification is found elevated, while PRS isoform-I expression is similarly higher on western blot analysis or in isoelectrofocusing electrophoresis. In contrast, PRS activity is usually low in red blood cells, which may be explained by enzyme lability in post-mitotic cells. PRPP and nucleotide levels are typically high in cells, as well [1,11]. The presence of a hemizygous pathogenic gain-of-function missense variant in *PRPS1* has been reported only in the superactive severe phenotype, involving less than 10 families to date [14]. Although PRS overactivity is an X-linked disorder, this diagnosis should also be considered in females, owing to the random X-inactivation. Only a few affected female patients have been reported to date, presenting with hyperuricemia, nephrolithiasis, and gout [15–17], while one female case has been described, presenting with sensorineural deafness [18]. The treatment primarily relies on lowering uric acid levels *via* xanthine oxidase inhibitors, along with a low-purine low fructose diet and high daily fluid intake, in addition to urine alkalinization so as to increase uric acid solubility. It must, however, be stressed that this management has no beneficial outcome on neurological symptoms, if present [1,11]. Yet, should this be the case, the diet supplementation that has recently been proposed to stabilize Arts disease might be helpful (see the next section).

3. Phosphoribosylpyrophosphate synthetase (PRS) deficiency

PRPP, the product of PRS, is not only the precursor of purine *de novo* synthesis but is required as well for purine salvage reactions catalyzed by HPRT and APRT (adenine phophoribosyltransferase). Consequently, PRS deficiency causes a purine nucleotide depletion in the body. In contrast, there is no pyrimidine depletion in PRS deficiency even if PRPP is also required for UMPS (uridine monophosphate synthase) activity in the last step of pyrimidine biosynthesis (Fig. 1). This is explained because, unlike purines, diet-derived pyrimidines are allowed to enter directly the blood circulation and UMP salvage pathway does not require PRPP [19]. Three independent clinical phenotypes have initially been described on account of PRS deficiency. While linked to the presence of loss-of-function variants in *PRPS1* gene, these phenotypes represent a continuum disease spectrum, being correlated with the residual enzyme activity, as well as X-chromosome inactivation patterns in affected females [10,20,21]. Arts syndrome is the most severe form [22] and X-linked non-syndromic hearing loss (DFNX1, also called DFN2) [23] the milder form, with Charcot-Marie-Tooth disease 5 (CMTX5, also called Rosenberg-Chutorian syndrome) being in-between [24]. Sensorineural hearing loss is a common feature, which can either be present alone like in DFNX1 or be associated with ataxia, hypotonia, peripheral neuropathy (due to demyelination and axonal loss) and optic neuropathy, as seen in CMTX5 and Arts syndromes. The latter is more severe, owing to intellectual disability, delayed motor development, and immune system dysfunction being characterized by recurrent respiratory infections and early death in affected patients [1]. Remarkably, a very severe phenotype has been reported in two male siblings displaying intrauterine growth retardation and high maternal alpha-fetoprotein levels, facial dysmorphia, severe intellectual impairment, spastic quadriparesis, short stature, diabetes insipidus, as well coloboma-like lesions along with retinal dystrophy [25]. Female carriers may develop similar symptoms, which are usually milder, including hearing loss, retinal dystrophy, or cerebellar ataxia [1,26–28]. A low PRS activity in red blood cells, fibroblasts, or lymphoblasts, along with the presence of pathogenic variants in *PRPS1,* is sufficient to establish the diagnosis. To date, only missense variants have been reported. Laboratory features, which have been mostly described in severe phenotypes, consist of low blood uric acid, low urinary levels of hypoxanthine, a slight elevation of orotic acid excretion in urine, as well as low GTP, ATP, NAD and NADP levels in erythrocytes [1,25,29]. Diet supplementation with S-adenosyl-methionine (SAM), which is a PRS-independent source of nucleotide precursors that freely crosses the gut and blood-brain barriers, has been shown to reduce hospitalization days while stabilizing ataxia and hearing loss in two patients [1,29,30]. Likewise, a co-supplementation with nicotinamide riboside, which similarly is a PRS-independent precursor of NAD and NADP, has recently displayed encouraging results in a single patient suffering from Arts syndrome, while further improving his clinical phenotype, as well as T-cell survival and function [29]. Additional studies are necessary to corroborate these effects, and include less severe PRS-deficient phenotypes.

4. Bifunctional phosphoribosylaminoimidazole carboxylase/ phosphoribosylaminoimidazole-succinocarboxamide synthetase (PAICS) deficiency

PAICS catalyzes Steps 6 and 7 in the *de novo* purine biosynthesis pathway (Fig. 1). So far, only a single report described two siblings from the Faroe Islands affected with PAICS deficiency. The respective pregnancies were characterized by polyhydramnios and intrauterine growth retardation. Severe and complex malformations consisted of multiple skeletal malformations, short neck and short stature, flat face with hypertelorism, nasal hypoplasia and choanal atresia, pulmonary hypoplasia, esophagus atresia, and genitourinary abnormalities, resulting in early death on Days 2 or 3. The enzyme activity was not completely abolished, strongly suggesting that null mutations are incompatible with life [31]. Aminoimidazole ribotide (AIR), which is the PAICS substrate, along with its dephosphorylated form aminoimidazole riboside (AIr), were previously shown to accumulate in the growth media of PAICS-deficient cell models [32], whereas they were not detected in skin fibroblasts of affected individual. However, these compounds may possibly be increased in body fluids. Additional reports are necessary to further characterize the clinical picture of this metabolic disorder.

5. Adenylosuccinate lyase (ADSL) deficiency

ADSL catalyzes two different steps pertaining to purine synthesis, comprising the conversion of SAICAR into AICAR (Step 8), along with the *de novo* pathway, as well as the conversion of S-AMP into AMP (Fig. 1). Two recent publications involving 24 patients have increased the number of reported ADSL-deficient patients to around 120, with over different 70 mutations identified [33,34]. The clinical spectrum is broad, ranging from fatal neonatal presentations to milder forms comprising four major phenotypes [35,36]. The neonatal form presents with encephalopathy, lack of spontaneous movements, respiratory failure, and intractable seizures, all of which result in early death within the first weeks of life. The most common form that was previously described as “Type I" manifests itself within the first months of life and is characterized by severe psychomotor retardation, early onset seizures, autistic features, growth retardation, and microcephaly (“Rett-like syndrome”). The moderate form that was previously described as “Type II" is characterized by psychomotor retardation and by autistic features and stereotypies. A fourth milder phenotype manifesting itself with only isolated psychomotor delay or ataxia has similarly been reported [37] (& personal unpublished observations). Brain imaging reveals unspecific findings, including atrophy of the cerebral cortex, corpus callosum, and cerebellar vermis, as well as white matter anomalies like delayed or lack of myelination. The succinylpurines SAICAriboside (SAICAr) and S-Adenosine (S-Ado), representing the dephosphorylated counterparts of the two substrates, accumulate in body fluids of affected patients. The S-Ado/SAICAr ratio is commonly around one in severe forms of ADSL deficiency, and between two and four in milder phenotypes, depending of the inherent properties of mutated enzymes [38]. Although the mechanisms underlying the psychomotor retardation remain unexplained, SAICAr is suggested to exert a toxic effect, which is counteracted by S-Ados protective effect. Treatment is nonspecific and consists primarily in managing epilepsy, while using the beneficial effects of a ketogenic diet for certain patients [36].

6. Bifunctional aminoimidazole-carboxamide riboside transformylase/ IMP cyclohydrolase (ATIC) deficiency

Bifunctional AICAR transformylase/IMP cyclohydrolase (ATIC) catalyzes the last two reactions (Steps 9 and 10) in the *de novo* purine biosynthesis pathway (Fig. 1). Only five patients originating from four families have been reported so far [34,39,40]. Clinical features comprise intrauterine growth retardation, severe neurodevelopment impairment, visual impairment due to chorioretinal atrophy, severe scoliosis, facial dysmorphia, as well as drug-resistant epilepsy. One patient presenting with a less severe phenotype and without epilepsy was shown to be able to say a few words and to stand up with support at age seven. Aortic coarctation and hepatic alteration were also reported in affected individuals. High urinary levels of 5-amino-4-imidazolecarboxamide-riboside (AICAr), which is the dephosphorylated counterpart of AICAR (also called ZMP), meaning ATIC's substrate, is a key feature of the disease. Succinylpurines are usually found elevated, as well, although SAICAr may at times remain in the normal range [39,40]. The final diagnosis relies upon *ATIC* molecular analysis.

7. ADSS, muscular isoform deficiency (*ADSSL1*)

Adenylosuccinate synthase (ADSS) catalyzes the initial conversion step of IMP into AMP (Fig. 1). Four patients originating from two Korean families were initially identified by whole exome sequencing. These patients were affected by distal myopathy, sharing compound heterozygous pathogenic variants in *ADSSL1* [41]. Notably, this gene encodes a muscle-specific isoform of ADSS, which is mainly expressed in skeletal and heart muscles [42]. At a later stage, a large Japanese cohort involving 63 patients from 59 families was identified [3]; their diagnosis was confirmed, with two common pathogenic variants revealed as founder mutations in Japanese and Korean ethnicities (c.781G > A and c.919delA). This large cohort was characterized by a myopathy phenotype, which usually started during adolescence. Muscle weakness progressed slowly, and muscle symptoms were related to affected proximal or distal leg muscles, facial muscles, upper limb muscles, as well as diaphragm, tongue, and para-spinal muscles. A significant number of patients developed respiratory insufficiency, dysphagia, and left ventricle hypertrophy. Nemaline bodies, increased lipid droplets, and myofibrillar disorganization were the typical features on histological muscle examination. Magnetic resonance imaging (MRI) of muscles displayed diffuse fatty infiltration, especially involving leg and tongue muscles, slowly progressing with age. Mean creatine kinase levels were usually reported to be about twice the upper normal values. To date, ADSSL1-related myopathy has also been reported in patients from Turkish and Indian origins [43]. Interestingly, a pathogenic homozygous frameshift *ADSSL1* variant was associated with a severe phenotype characterized by congenital joint contractures and an even more severe neurological phenotype (fetal akinesia) in a Turkish patient [44]. This suggests that loss of function variants in this gene could be associated with more severe phenotypes.

8. Inosine triphosphate pyrophosphatase (ITPase) profound deficiency

Inosine triphosphate pyrophosphatase catalyzes the conversion of (deoxy-)ITP into (deoxy-)IMP and of (deoxy-)XTP into (deoxy-)XMP in order to remove non-canonical (deoxy-)nucleotide triphosphates. (Deoxy-)ITP/XTP are byproducts generated either by wrong phosphorylation of IMP or XMP or by deamination of (deoxy-)ATP/GTP [4] (Fig. 1). Profound ITPase deficiency has been reported in patients presenting with severe infantile encephalopathy (Martsolf-like syndrome),

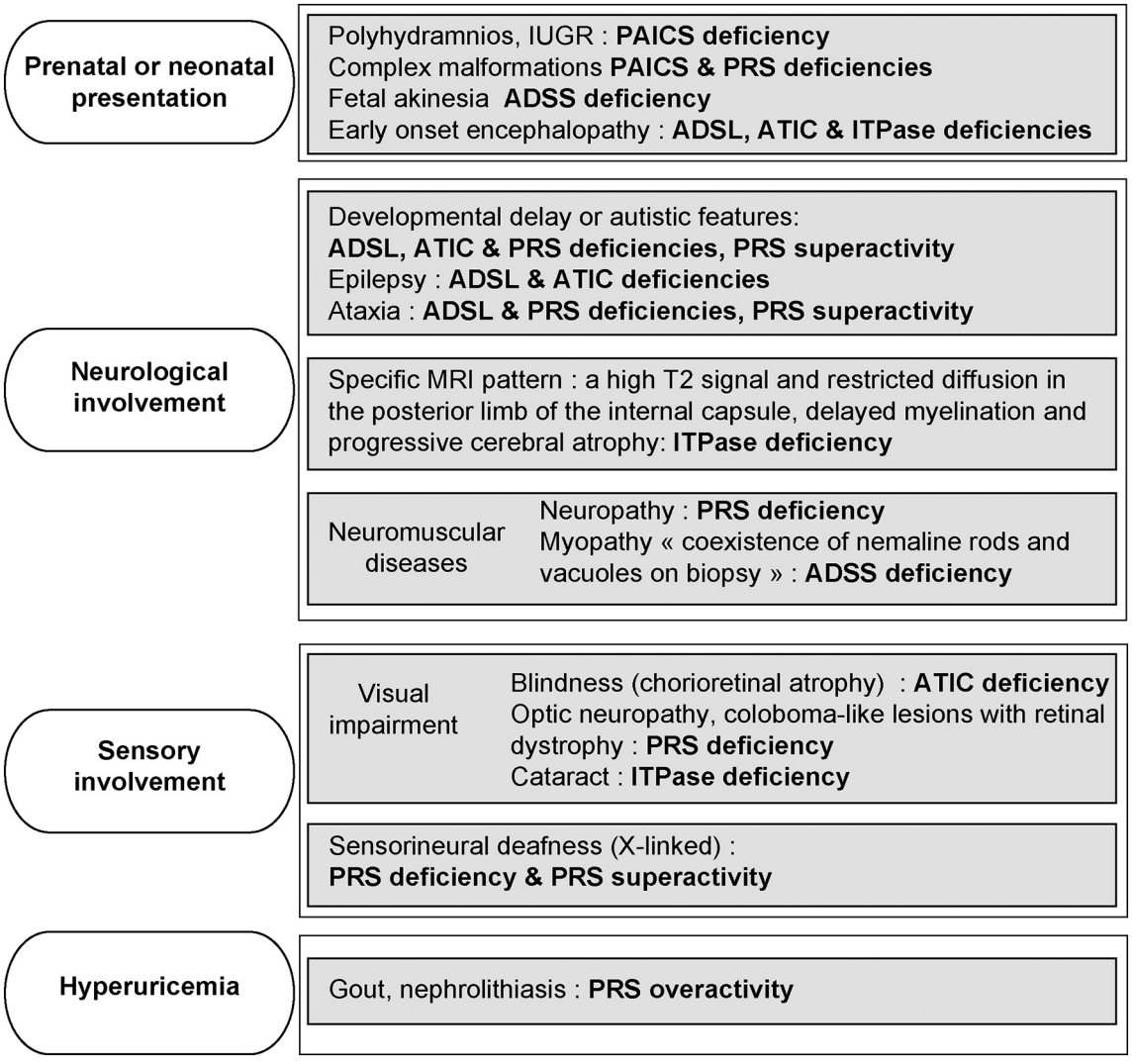

Fig. 2. Main clinical signs encountered in purine biosynthesis disorders.
This flowchart highlights the symptoms most commonly associated with disorders of purine biosynthesis. Neurological involvement is quite common but not always very specific. Dysmorphic signs are also described in some patients (PRS overactivity or deficiency, ATIC deficiency), as well as cardiac (ATIC and ITPase deficiencies) or hepatic impairment (ATIC deficiency).

developmental delay, progressive microcephaly, epilepsy, bilateral cataract, cardiomyopathy, and early death [45,46]. These patients share a distinct brain MRI pattern characterized by a high T_2 signal and restricted diffusion in the posterior limb of the internal capsule in combination with delayed myelination and progressive cerebral atrophy [45–47]. This severe phenotype confirmed the previously reported description of *ITPA* knock-out mouse model. Indeed, ITPAse-deficient mice exhibited early death before the age of 2 weeks, associated with severe neurological and cardiac impairment. The severity of this disease is probably explained by the unwanted incorporation of (deoxy-)ITP/XTP into nucleic acids [48], in addition to a possible interference with protein reactions using ATP or GTP, causing programmed cell death [5]. Accordingly, ITPase is paramount to avoid errors in genetic transmission and to prevent metabolic perturbations, as well, which is an illustration of metabolite repair mechanism [49]. In contrast to this very severe phenotype, *ITPA* polymorphisms resulting in partial or even total loss of ITPase activity and ITP accumulation in red blood cells without a clinical phenotype in humans had previously been reported. These variants were considered to be the cause of adverse drug reactions to methotrexate, mercaptopurines, and thiopurine prodrugs [50–52]. Therefore, the assessment of ITPase activity or increased ITP concentrations in red blood cells does not permit to discriminate between pathogenic variants leading to profound ITPase deficiency and those of pharmacogenetics relevance.

9. Discussion

Inborn errors of metabolism affecting the purine synthesis pathways are extremely rare, with clinical signs that are often unspecific (Table 1 and Fig. 2), which likely explains the low number of such patients reported so far. With the development of genetic analyses (WES, WGS), new deficits have been discovered (PAICS and muscular ADSS deficiencies). Likewise, the clinical phenotype of certain defects has been better described, emphasizing the presentation which is sometimes not very specific for already known diseases (example: slight psychomotor retardation in ADSL deficiency). The clinical presentation is broad but some elements may point to a diagnosis of a purine synthesis defect and are synthesized in Fig. 2.

Several mechanisms are likely involved in the large diversity of phenotypes observed in the disorders affecting the same pathway. Since intermediates in *de novo* purine synthesis display additional functions in intracellular pathways, their abnormal accumulation in specific cells is expected to cause disturbances in signaling pathways. SAICAR is known to bind to pyruvate kinase M2 (PKM2), inducing a protein kinase activity of the enzyme and interfering with transcription factors. This is particularly of interest in cancer cell metabolism and proliferation [53] but also potentially in the pathophysiology of ADSL deficiency and to a lesser extent in ATIC deficiency [54]. Similarly, AICAR (ZMP), which accumulates in ATIC deficiency, is known to activate the protein kinase AMPK, a key energy homeostasis regulator [39]. The predicted AIR accumulation inside PAICS deficient cells is expected as well to interfere with cellular signaling. Interestingly, AIr has been shown to exert an even higher cytotoxicity than SAICAr in cell models [31]. Furthermore, purinergic receptors activation, which is critical for neurodevelopment, is expected to be severely disturbed due to aberrant purinergic signaling in inborn errors of purine metabolism [55]. Finally, epistatic connections are another mechanism to consider in the large diversity of phenotypes observed.

On account of the non-specific neurological presentation of ADSL, ATIC, and PAICS deficiencies, their diagnosis primarily relies on urinary purine analysis or molecular analysis [56]. Untargeted metabolomics approach is another promising and complementary direction, enabling the detection of new specific biochemical markers that are still lacking or not confirmed in classical biological fluids (urine and plasma/serum) especially for PRS, PAICS, muscular ADSS and ITPase deficiencies. The implementation of untargeted or expanded targeted metabolomics screening methods using high-resolution and high-accuracy mass spectrometry in biochemical genetics laboratories has also the potential to screen for uncommon metabolites such as AICA-riboside (not always screened in classical targeted methods) or presumably AI-riboside for the diagnosis of ATIC and PAICS deficiencies, respectively. These approaches of high technology combined to genetic tests will most probably improve the diagnostic rate of hereditary metabolic diseases compared to the use of classical targeted tests alone [34,57].

To date, no patient has been described affected by a defect pertaining to one of the first five steps of the *de novo* purine biosynthesis pathway. The first reason accounting for this could be that a defect involving the early stages of *de novo* synthesis is likely to be incompatible with life. Indeed, this hypothesis is in line with the relatively low numbers of predicted loss-of-function (pLoF) variants observed in gnomAD databases compared to the expected numbers, especially concerning the gene *PPAT* (only three observed pLoF variants *versus* 26.2 expected ones). In accordance with this, PFAS (Step 4) deficiency has been incriminated to be responsible for early embryonic lethality in a breed of dairy cattle [58]. Moreover, the only humans suffering from PAICS (Steps 6 and 7) deficiency reportedly died within the first days of life [29]. A second reason explaining the few numbers reported may be either a lack or an instability of potential biochemical markers underlying these defects [54].

Finally, the last concern pertains to the availability of an effective treatment for these disorders. A better understanding of the underlying pathophysiological mechanisms, along with an earlier diagnosis, may be a good direction to take even if some of these diseases are associated with congenital malformations or severe irreversible neurological impairment.

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