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CASE REPORT

Expanding the spectrum of clinical severity of AICA-ribosiduria: Report of two siblings with mild phenotype caused by a novel pathogenic variant in ATIC gene

Jessica Galli[1,2] | Enza Maria Valente[3] | Joseph Dewulf[4] | Alessandra Franzoni[5] | Sandrine Marie[4] | Massimo Plumari[6] | Federica Zanetti[1] | Elisa Fazzi[1,2]

[1]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy

[2]Unit of Child Neurology and Psychiatry, ASST Spedali Civili of Brescia, Brescia, Italy

[3]Department of Molecular Medicine, University of Pavia and Neurogenetics Research Center, IRCCS Mondino Foundation, Pavia, Italy

[4]Laboratoire des Maladies Métaboliques Héréditaires/Biochimie Génétique et Centre de Dépistage Néonatal, Cliniques Universitaires Saint-Luc, Brussels, Belgium

[5]Department of Neurological and Vision Sciences, ASST Spedali Civili of Brescia, Brescia, Italy

[6]Neurogenetics Research Center, IRCCS Mondino Foundation, Pavia, Italy

Correspondence
Jessica Galli, Unit of Child Neurology and Psychiatry, ASST Spedali Civili of Brescia, Piazzale Spedali Civili, 1, 25123, Brescia, Italy.
Email: jessica.galli@unibs.it

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Abstract

5-Amino-4-imidazolecarboxamide-ribosiduria (AICA-ribosiduria) is an extremely rare inborn error of purine biosynthesis metabolism caused by pathogenic variants in ATIC gene that encodes a protein catalyzing the last steps of the de novo purine biosynthesis. To date, only six cases have been reported presenting a severe phenotype characterized by coarse facies and variable dysmorphic features, intrauterine and postnatal growth retardation, severe and early neurodevelopment delay, profound congenital visual deficit, scoliosis and, less frequently, epilepsy, aortic coarctation, chronic hepatic cytolysis, nephrocalcinosis and mild genitalia malformation. In this article, we report two new cases of AICA-ribosiduria carrying new pathogenic variants in *ATIC* (c.421C>T;p.Arg141Ter and c.1753A>G p.Thr585Ala) associated to a milder phenotype compared to previously reported patients. Particularly, the children showed few dysmorphic features (bulging forehead, depressed nasal bridge, and flat nasal tip), postnatal growth impairment, psychomotor delay since the second year of life, reduction of visual acuity (from mild impairment to low vision from the age of 5 years and to partial blindness from the age of 7 years) and mild hepatic dysfunctions. Scoliosis as well as epilepsy, renal involvement, or genitalia malformation were not detected. According to literature data, we found an abnormal accumulation of intermediates of de novo purine biosynthesis in the urine of both siblings. This report expands the spectrum of phenotypic severity associated to ATIC biallelic pathogenic variants and prompts the need to investigate ultra-rare causes of metabolic disorders such as AICA-ribosiduria in subjects with early neurological and sensory involvement of uncertain etiology.

KEYWORDS
AICA-ribosiduria, ATIC deficiency, de novo purine biosynthesis, intellectual disability, retinal dystrophy, visual impairment

1 | INTRODUCTION

5-Amino-4-imidazolecarboxamide-ribosiduria (AICA-ribosiduria) is an extremely rare inborn error of purine biosynthesis metabolism characterized by coarse facies and variable dysmorphic features, growth retardation (intrauterine and postnatal), neurodevelopment delay involving both motor and language skills, severe visual deficit and scoliosis. Additional features present only in a subset of patients

include early onset epilepsy, aortic coarctation, chronic hepatic cytolysis, nephrocalcinosis, and mild genitalia malformation (Ramond et al., 2020). AICA-ribosiduria is caused by recessive pathogenic variants in the *ATIC* gene on chromosome 2q35 (Micheli et al., 2011), encoding a protein called "Bifunctional purine biosynthesis protein ATIC". This protein product catalyzes the last steps of de novo biosynthesis of purines, essential components of several vital biomolecules, such as nucleic acids, coenzymes, signaling and chemical energy transfer molecules (Dewulf et al., 2022). Specifically, *ATIC* mutations lead to accumulation of 5-amino-4-imidazolcarboxamide-riboside (AICA-riboside), succinyl-5-amino-4-imidazolecarboxamide-riboside (SAICA-riboside), and succinyladenosine (S-Ado) in biofluids, that are intermediates of de novo purine biosynthesis (Marie et al., 2004). The pathological mechanism needs to be clarified, but it is hypothesized that the abnormal accumulation of these intermediate molecules could exert a cytotoxic effect (Baresova et al., 2012). To date, only six patients (Joy et al., 2022; Liu et al., 2021; Marie et al., 2004; Ramond et al., 2020) from five families have been reported and the diagnosis is based on the presence of high urinary levels of AICA riboside, SAICA riboside, and S-Ado, and on molecular analysis of the *ATIC* gene.

In this paper, we describe two siblings with AICA-ribosiduria carrying novel pathogenic variants in *ATIC* associated to a milder phenotype compared to previously reported patients.

2 | CLINICAL REPORT

We recruited two patients from the Neuro-ophthalmological Tertiary Centre of Child Neurology and Psychiatry Unit, Civil Hospital of Brescia. They came to our attention at 2 months of age for jerky nystagmus. We got written informed consent from parents in order to conduct genetic testing and to take photographs for publication. We carried out longitudinal evaluations on neurological aspects, neurodevelopmental profile, cognitive and adaptive functions, and visual skills every year from the first months of life to 9 years of age (for the proband) and to 6 years (for his sister).

We performed whole-exome sequencing (WES) using Twist Human Core Exome Kit (Twist Bioscience) on a NovaSeq 6000 platform (Illumina, San Diego, CA). Variants were filtered and prioritized as previously described (PMID 34846692), and relevant variants were segregated in parents using Sanger sequencing.

2.1 | Case N°1

The child was the second of healthy unrelated parents, with unremarkable family history. The pregnancy was marked by the threat of premature birth at 32 gestational weeks, so the mother was hospitalized for 2 days and treated with Ritodrine for 5 days. No intrauterine growth retardation was observed at ultrasonographic examination. The proband was born from natural delivery at the 38th week of gestational age: birth weight was 2840 g (10°p), length 47 cm (50°p), head circumference 33 cm (25°p). Neonatal examination was normal (Apgar score 9-9 at 1 and 5 min).

Early neurodevelopmental milestones were appropriately acquired (smile at age of 2 months, head control at 3; independent sitting at 7; grasping at 4 and babbling at 8 months) but a psychomotor delay became evident from the second year of life (independent walking at 25 months, running and jumping at 4 years; first words at 21 months with a slow progression of vocabulary acquisition, consisting of 30 words at 3 years of age, two words combination at 4 years of age and sentences production over 6 years of age). Yearly general and neurological examination conducted from age 6 months showed facial dysmorphic features such as prominent and bulging forehead, depressed nasal bridge and flat nasal tip (see Figure 1), and persisting global hypotonia, while no scoliosis or other skeletal disorders were observed. From age 2 months, postnatal growth retardation was observed (weight and height <3°percentile) while head circumference remained within normal range.

The neurodevelopmental profile assessed using the Griffiths Mental Development Scales-Extended Revised (GMDS-ER) (Griffiths & Huntley, 1996), revealed normal scores on General Quotient and on all the subscales (Locomotor, Personal-Social, Hearing and Speech, Eye and Hand Coordination, Performance and Practical Reasoning) at 7 months, while these became delayed at 21, 33, and 45 months (see Table 1). The cognitive and adaptive evaluations performed at ages 7 and 9 years using the Wechsler Intelligence Scales IV edition (Wechsler, 2003) and the Vineland Adaptive Behaviour Scales-II (VABS-II) (Sparrow et al., 2016) respectively, showed mild intellectual disability and impairment of adaptive functioning (see Table 1).

From 6 months of age, he underwent a yearly neurovisual evaluation according to our optimized protocol (Fazzi et al., 2021; Galli, Loi, Molinaro et al., 2022). A persisting mild hypermetropia, progressive retinal dystrophy (7 months: retinal pigment epithelium (RPE) rearrangement, 13 months: whitish optic disc in both eyes, patchy macular dystrophy with RPE rearrangement surrounded by black area, and reduced caliber of the vessels), disorders of oculomotor functions characterized by horizontal jerky nystagmus, unstable fixation, discontinued smooth pursuit and saccades dysfunctions were observed. Visual acuity was mild impaired from the first months of life to 3.5 years of age, then a progressive worsening of visual acuity characterized by partial blindness was observed (see Figure S1, supplementary material), contrast sensitivity was normal at each evaluation (Hiding Heidi Low Contrast Face Test: 1.25%). Electrophysiological examinations performed at age 2 years confirmed the damage of photoreceptors (electroretinogram: reduced amplitude; visual evoked potential: reduced amplitude and increased latency compared with age-matched healthy controls). Ocular coherence tomography (OCT) and retinography (8 years old) revealed a panretinal degeneration without oedema, patchy macular dystrophy, thinning of the macular retinal layers and loss of photoreceptor layer (see Figure 1).

A mild chronic increase of transaminase levels was documented from 21 months of age (aspartate aminotransferase/alanine aminotransferase of 81/136 and 138/181 U/L at 21 months and 43 months respectively, normal <37), and the abdominal ultrasound performed at 3.5 years revealed mild hepatomegaly and steatosis. Triglycerides,

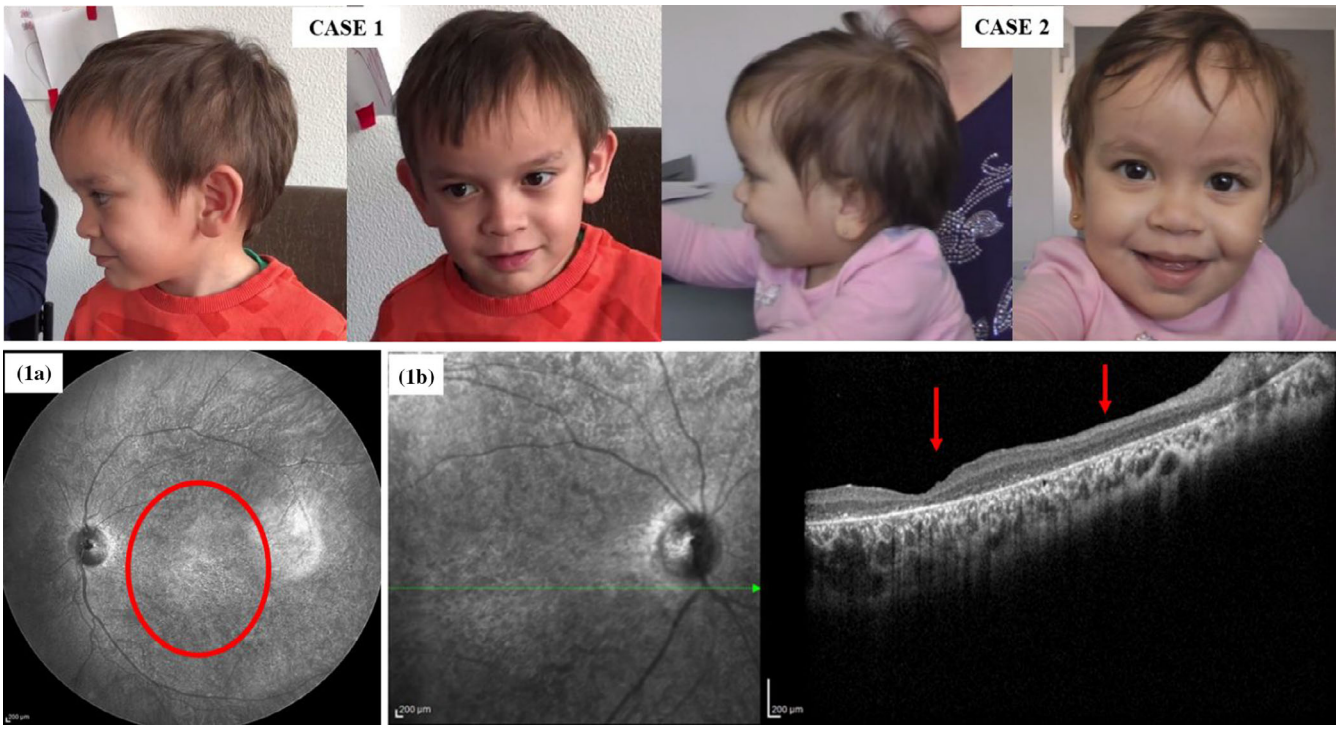

FIGURE 1 Facial profile (front and side) from case 1 (5.5 years old) and case 2 (2 years old) showing dysmorphic features: Prominent and bulging forehead, depressed nasal bridge and flat nasal tip. (a) Retinography of case 1 showing a panretinal degeneration and patchy macular dystrophy (red circle). (b) Ocular coherence tomography of case 1 revealing thinning of the macular retinal layers and loss of photoreceptor layer (red arrows)

cholesterol, creatinine and azotemia, urinary and plasmatic amino acid and urinary organic acids were normal. Electrocardiogram and heart ultrasound performed at 21 months of age were negative.

No clinical seizures were reported, and the electroencephalogram and brain magnetic resonance imaging (performed at 3 months of age and 5 years) were normal. Fragile X testing and 180 k array-CGH were negative. Upon filtering, WES revealed two compound heterozygous variants in the *ATIC* gene (c.421C>T;p.Arg141Ter and c.1753A>G p.-Thr585Ala), classified as pathogenic/likely pathogenic according to ACMG criteria, and inherited from mother and father respectively (see Figure S2, supplementary material for sequencing chromatogram). To confirm the molecular findings, a metabolic investigation of urines by UPLC-PDA was performed, which revealed abnormal levels of AICA-riboside (79.9 mmol/mol creatinine, normal 0.00), SAICA-riboside (25.7 mmol/mol creatinine, normal <0.1) as well as S-ado (17.0 mmol/mol creatinine, normal <5). Interestingly, purine and pyrimidine analysis on plasma revealed very low, barely detectable levels (AICA-riboside 0.17 μM, SAICA-riboside 0.77 μM, and S-Ado not detectable).

2.2 | Case N°2

The patient was the younger sister of case 1. Pregnancy was characterized by early uterine contractions at 34 gestational weeks. She was born from natural delivery at 37, 2nd week of gestational age: birth weight was 2410 g (10°p), length 43 cm (3–10°p), head circumference 32,5 cm (10°p). Neonatal examination was normal and Apgar score was 10 at 1′ and 5′. A small hemodynamically non-significant muscular middle interventricular defect and patent foramen ovale (confirmed at echocardiographic control) was reported.

She appropriately acquired early developmental milestones (smile at age of 2 months, head control at 3; independent sitting at 8; grasping at 4 and babbling at over 8 months) but independent walking was achieved at 21 months, running and jumping at 3 years and 10 months. She pronounced the first words at 11 months with slow vocabulary acquisition (about 20 words at 3 years of age, simple sentences at 6 years) with dyslalia. General and neurological examination from age 6 months revealed facial dysmorphic features such as a prominent and bulging forehead, depressed nasal bridge and flat nasal tip (see Figure 1) and global hypotonia. Postnatal growth was persistently at the lower limits of normality (weight and height 10–25°percentile), while head circumference was at the upper limits (75–90°percentile).

The neurodevelopmental profile assessed using GMDS-ER showed a progressive worsening of the psychomotor skills from borderline scores at 7 months of age to delayed scores from 18 months of age onwards (see Table 1). The cognitive and adaptive evaluations performed at age 6 years using the Wechsler Intelligence Scales III edition (Wechsler, 2002) and VABS-II respectively, showed mild intellectual disability and low adaptive skills (see Table 1).

TABLE 1 Developmental, cognitive, and adaptive profile of the two siblings

		Developmental profile (GMDS-ER)						
Case	Age (mo)	GQ	Motor	P/Social	H/Speech	E/Hand	Performance	P. Reason
N.1	7	92	84	99	100	89	91	/
	21	<50	<50	<50	<50	<50	<50	/
	33	<1°	<1°	<1°	<1°	<1°	<1°	<1°
	45	<1°	<1°	<1°	<1°	<1°	<1°	<1°
N.2	7	74	66	66	91	67	84	/
	18	<50	<50	<50	<50	66	<50	/
	24	<50	<50	59	52	<50	70	/
	37	<1°	<1°	<1°	<1°	<1°	<1°	<1°

		Cognitive level (standard Score)					Adaptive skills (°)			
	Age (yrs)	FSIQ	VCI	PRI	VMI	PSI	Total	Com	Dls	Soc
N.1	7	53	74	54	73	56	0.5	<0.1	2	9
	9	59	78	63	67	68	0.5	<0.1	2	9
N.2	6	68	58	80	/	56	8	4	25	10

Note: The development profile was evaluated in both patients using the GMDS-ER. The quotients (Total score and score of each domain) are reported in standard scores when the child was ≤24 months old (Total score: mean 100 ± 12; Score of each domain: mean 100 ± 16. Scores >-1DS: normal, between -1DS and -2DS: borderline; < -2DS: delayed) and in centiles when the child was >24 months (Scores <1°: delayed). The cognitive level was assessed using age-appropriate versions of Wechsler intelligence scales (WISC-IV in case 1 and WPPSI-III in case 2). All the quotients are reported in standard scores (mean 100, SD 15). Patients are rated as follows: more than−1DS, normal; between -1DS and -2DS, borderline; less than−2DS, delay. The assessment of adaptive skills was performed using VABS II (scores of each domain were expressed in percentiles; adaptive disorders were present for those domains with a centile score <5 degrees).

Abbreviations: Com: communication; Dls: daily living skills; E/Hand: Eye & Hand Coordination; FSIQ: Full Scale Intelligence Quotient; GQ: general quotient; H/Speech: Hearing & Speech subscale; mo: months; motor: locomotor subscale; N.: number; P. Reason: practical reasoning; PRI: perceptual reasoning; PSI: Processing Speed Index; P/Social: personal-social subscale; Soc: socialization; Total: total score; VCI: verbal comprehension; WMI: working memory; yrs: years.

From age 5 months, she yearly underwent neurovisual evaluation that showed persisting mild hypermetropia, progressive retinal dystrophy (5 months: RPE rearrangement, 8 months: patchy macular dystrophy with RPE rearrangement surrounded by black area), disorders of oculomotor functions characterized by horizontal jerky nystagmus, unstable fixation, discontinued smooth pursuit and saccades dysfunction. Visual acuity was mildly impaired from the first months of life to 3.5 years of age, then a progressive worsening of visual acuity characterized by low vision was observed (see Figure S1, supplementary material), while contrast sensitivity was normal (1.25%). Electrophysiological examinations at 7 months of age confirmed the damage of photoreceptors (electroretinogram: reduced amplitude; visual evoked potential: reduced amplitude and increased latency compared with age-matched healthy controls).

Liver enzymes were normal at 7 months and mildly increased at 7 years (aspartate aminotransferase and alanine aminotransferase of 38 and 48 U/L respectively, normal <32); triglycerides, serum creatinine, azotemia, and abdomen ultrasound were normal. Electroencephalogram (performed at 14 months of age) and brain MRI (2 years and 7 months of age) were negative. WES disclosed the same compound heterozygous variants in *ATIC* as her affected brother. Metabolic investigations of urines revealed elevated levels of AICA-riboside (78.7 mmol/mol creatinine), SAICA-riboside (19.2 mmol/mol creatinine), and S-Ado (15.5 mmol/mol creatinine). Similarly to her brother, purine and pyrimidine plasmatic levels were very low (AICA-riboside 0.22 μM, SAICA-riboside 0.78 μM, and S-Ado 0.13 μM).

3 | DISCUSSION

Purines play an essential role in the synthesis of RNA, DNA, coenzymes, signaling and energy transfer molecules (Dewulf et al., 2022). The pool of purine nucleotides is the result of a fine balance between their anabolism (de novo purine biosynthesis and salvage recycling) and their catabolism (degradation and urinary excretion). In humans, three enzyme defects (ADSL, PAICS, and ATIC deficiencies) may affect the de novo purine biosynthesis pathways, resulting in a broad spectrum of malformations, and neurological dysfunctions (Dewulf et al., 2022). Focusing on ATIC deficiency, nowadays only six patients have been described with a variable association of systemic signs and symptoms affecting growth (antenatal/postnatal growth retardation), brain (neurodevelopment delay/intellectual disabilities, epilepsy), eye (visual deficit due to chorioretinal atrophy), bone (scoliosis), liver (chronic hepatic cytolysis, hepatomegaly, and steatosis), kidney (nephrocalcinosis) and heart (aortic coarctation) (Joy et al., 2022; Liu et al., 2021; Ramond et al., 2020). In this paper, we described two siblings with AICA-ribosiduria carrying novel pathogenic variants in the ATIC gene associated with a milder phenotype compared to those reported in literature.

The children in this report presented few dysmorphic features consisting of prominent and bulging forehead, depressed nasal bridge, and flat nasal tip without other previously reported features such as synophris, hypoplastic ears, malar hypoplasia, or brachycephaly (Joy et al., 2022; Marie et al., 2004; Ramond et al., 2020). Of note, our patients also did not show intrauterine growth retardation, oligoamnios or neonatal hypotonia; global hypotonia and growth impairment were observed only postnatally, from sixth and second months of life, respectively.

They acquired appropriate early developmental milestones but, from 18 months, we observed a mild psychomotor delay involving both motor and language skills. Previously children reported with AICA-ribosiduria could neither stand and walk independently (Joy et al., 2022; Marie et al., 2004; Ramond et al., 2020) nor speak (Joy et al., 2022; Ramond et al., 2020), except for the production of a few words documented in one case (Marie et al., 2004). Conversely, our siblings achieved independent walking, jumping, and running and developed expressive language abilities (simple phrases composition). Their cognitive assessment showed mild intellectual disability, different from the severe/profound impairment reported in former cases (Joy et al., 2022; Marie et al., 2004; Ramond et al., 2020). No data on developmental milestones and cognitive levels are available for the individual reported by Liu et al. (2021), therefore, we cannot assume that he/she had a severe delay like the first five described cases or a mild impairment as our two children. Both our patients presented low adaptive behavior performance regarding communication, organization of daily living activities, and socialization skills. No data are available on adaptive functions in subjects affected by AICA-ribosiduria, but we hypothesize that their impairment could be related to the limitations derived from the cognitive disorder itself and from the visual deficit, as observed in other clinical populations (Galli, Loi, Morandi, et al., 2022). In this regard, the older child affected by partial blindness showed a more severe adaptive deficit compared to his sister with low vision.

The longitudinal neurovisual evaluation revealed mild hypermetropia, horizontal jerky nystagmus and progressive worsening of visual acuity after 3 years of age evolving to low vision at 5 years and partial blindness from 7 years of age onwards. The severe visual impairment could be explained by a progressive involvement of retina, consisting of panretinal degeneration, patchy macular dystrophy, thinning of the macular retinal layers, and loss of photoreceptor layers. They were able to fix a target and perform smooth pursuit and saccadic movements, even if the performance was extremely discontinued. Yet, as for other clinical aspects, their visual acuity values were not as severe as the congenital light perception/blindness described in previous studies (Joy et al., 2022; Marie et al., 2004; Ramond et al., 2020). A possible explanation is that the chorioretinal atrophy took place at an early stage and retinal involvement was limited to cones while rods, destroyed in other reported cases (Ramond et al., 2020), there seemed to be spared.

In his patients, Ramond et al. (2020) also described epilepsy, skeletal disorders, genital malformation, and in about half of cases cardiovascular defects, renal abnormalities, and brain malformation. Our children did not suffer from any of these diseases/malformations; only a small muscular middle interventricular defect and patent foramen ovale were observed in the younger sibling. As well as some other cases, our patients had hepatic disorders characterized by a mild increase of transaminase levels associated in one case with hepatomegaly and steatosis. Consistent with the literature findings (Joy et al., 2022; Marie et al., 2004; Ramond et al., 2020), we found an abnormal accumulation of AICA-riboside, SAICA-riboside, and S-Ado in the urine of both siblings.

The reason underlying this variable spectrum of severity in ATIC-mutated patients remains to be understood. Seven reported patients (no information on the type of ATIC-mutation is available for the patient described by Liu and colleagues) are compound heterozygous and carry one bona fide loss of function allele (either frameshift or truncating variants, or lack of transcript due to a still unidentified variant) combined with a missense variant. Four out of seven patients, all with a severe phenotype, carry the same recurrent missense variant c. 1277A<G; p.Lys426Arg, which is consistently predicted as pathogenic by all software with a CADD score of 31. A fifth patient, also presenting the severe phenotype, carried the missense c.406G>A; p.-Ala136Thr variant, also consistently predicted as pathogenic with a CADD score of 29. The two siblings reported here, the only ones with a milder phenotype, carry the novel missense variant p.Thr585Ala, which is predicted as damaging but with a lower CADD score of 23. Further studies are needed to demonstrate whether the different missense variants might have a variable impact on enzymatic activity, resulting in variable residual enzymatic activity which in turn may influence the phenotypic manifestations of the disease. Indeed, our two patients seem to have lower urinary levels of AICA-riboside, SAICA-riboside, and S-ado compared to other patients (Ramond et al., 2020).

Even if the pathological mechanism of AICA-ribosiduria needs to be clarified, two different models have been proposed (Ramond et al., 2020). In the first one, the abnormal accumulation of AICA-riboside, SAICA-riboside, and S-Ado could exert a cytotoxic effect (Baresova et al., 2012) through, for example, the inhibition of lipids (Henin et al., 1995) and carbohydrate (Vincent et al., 1992) metabolism in the liver, stimulation of glucose uptake (Micheli et al., 2011), intracellular ATP depletion (Mazzarino et al., 2020). The second model suggests that the depletion of purine nucleotides during embryogenesis and organogenesis could determine devastating effects (Marie et al., 2004; Micheli et al., 2011). It has been hypothesized that purine synthesis during embryogenesis could be primarily dependent on de novo purine synthesis pathways, since the salvage recycling pathway may not completely compensate for a purine deficiency (Marie et al., 2004; Micheli et al., 2011). Central nervous system (CNS) seems to be particularly vulnerable to purine metabolic disorder since purines may modulate brain function: purine nucleotides and nucleosides are non-aminoacidic neurotransmitters with excitatory or inhibitory effect, depending on the region of the brain and the type of receptor involved (Burnstock, 2007; Micheli et al., 2011). Several studies underline the interconnection between brain damage and specific enzymatic deficiency including those involved in purine

metabolism (Micheli et al., 2011). Indeed, all patients including the two described here showed signs and symptoms of CNS involvement such as hypotonia, developmental delay, and intellectual disability.

In conclusion, this report expands the spectrum of phenotypic severity associated to *ATIC* biallelic pathogenic variants, and defines the core phenotype of AICA-ribosiduria, as characterized by growth retardation, hypotonia and developmental delay, intellectual disability, visual impairment characterized by hypermetropia, nystagmus, visual acuity deficit due to chorioretinal atrophy and liver dysfunctions. The disease seems to be slowly progressive since some signs and symptoms were not or only mildly evident at birth and became more severe from the first years of age. These observations prompt the need to investigate ultra-rare causes of metabolic disorders such as AICA-ribosiduria in subjects with early neurological and sensory involvement of uncertain etiology.

AUTHOR CONTRIBUTIONS

Jessica Galli, Enza Maria Valente conceived the study, wrote the manuscript and participated to data analysis. Massimo Plumari performed the genetic analysis. Sandrine Marie and Joseph Dewulf performed the metabolic investigation of urines and plasma and reviewed the manuscript. Alessandra Franzoni, Elisa Zanetti, and Jessica Galli performed the clinical evaluation, participated to image analysis, and contributed to manuscript editing. Elisa Fazzi coordinated the design of the study and reviewed the manuscript. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST

The authors declare to have no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Jessica Galli https://orcid.org/0000-0002-3347-7548

REFERENCES

Baresova, V., Skopova, V., Sikora, J., Patterson, D., Sovova, J., Zikanova, M., & Kmoch, S. (2012). Mutations of ATIC and ADSL affect purinosome assembly in cultured skin fibroblasts from patients with AICA-ribosiduria and ADSL deficiency. *Human Molecular Genetics*, *21*(7), 1534–1543. https://doi.org/10.1093/hmg/ddr591

Burnstock, G. (2007). Purine and pyrimidine receptors. *Cellular and Molecular Life Sciences: CMLS*, *64*(12), 1471–1483. https://doi.org/10.1007/s00018-007-6497-0

Dewulf, J. P., Marie, S., & Nassogne, M. C. (2022). Disorders of purine biosynthesis metabolism. *Molecular Genetics and Metabolism*, *136*(3), 190–198. https://doi.org/10.1016/j.ymgme.2021.12.016

Fazzi, E., Micheletti, S., Calza, S., Merabet, L., Rossi, A., Galli, J., & Early Visual Intervention Study Group. (2021). Early visual training and environmental adaptation for infants with visual impairment. *Developmental Medicine and Child Neurology*, *63*(10), 1180–1193. https://doi.org/10.1111/dmcn.14865

Galli, J., Loi, E., Molinaro, A., Calza, S., Franzoni, A., Micheletti, S., Rossi, A., Semeraro, F., Fazzi, E., & CP Collaborative Group. (2022). Age-related effects on the spectrum of cerebral visual impairment in children with cerebral palsy. *Frontiers in Human Neuroscience*, *16*, 750464. https://doi.org/10.3389/fnhum.2022.750464

Galli, J., Loi, E., Morandi, A., Scaglioni, V., Rossi, A., Molinaro, A., Pasini, N., Semeraro, F., Ruberto, G., & Fazzi, E. (2022). Neurodevelopmental profile in children affected by ocular albinism. *Neuropediatrics*, *53*(1), 7–14. https://doi.org/10.1055/s-0041-1732430

Griffiths, R., & Huntley, M. (1996). *Griffiths mental development scales (revised)*. UK Test Agency Limited.

Henin, N., Vincent, M. F., Gruber, H. E., & Van den Berghe, G. (1995). Inhibition of fatty acid and cholesterol synthesis by stimulation of AMP-activated protein kinase. *FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology*, *9*(7), 541–546. https://doi.org/10.1096/fasebj.9.7.7737463

Joy, P., Madhuri, V., Palocaren, T., Das, S., Susan Cleave Abraham, S., Korula, S., Koshy, B., Jose, J., Chandran, M., & Danda, S. (2022). Case report of a rare purine synthesis disorder due to 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICAR) deficiency. *Brain & Development*, *44*(9), 645–649. S0387-7604(22)00085–7. Advance online publication. https://doi.org/10.1016/j.braindev.2022.05.004

Liu, N., Xiao, J., Gijavanekar, C., Pappan, K. L., Glinton, K. E., Shayota, B. J., Kennedy, A. D., Sun, Q., Sutton, V. R., & Elsea, S. H. (2021). Comparison of untargeted metabolomic profiling vs traditional metabolic screening to identify inborn errors of metabolism. *JAMA Network Open*, *4*(7), e2114155. https://doi.org/10.1001/jamanetworkopen.2021.14155

Marie, S., Heron, B., Bitoun, P., Timmerman, T., Van Den Berghe, G., & Vincent, M. F. (2004). AICA-ribosiduria: A novel, neurologically devastating inborn error of purine biosynthesis caused by mutation of ATIC. *American Journal of Human Genetics*, *74*(6), 1276–1281. https://doi.org/10.1086/421475

Mazzarino, R. C., Baresova, V., Zikánová, M., Duval, N., Wilkinson, T. G., 2nd, Patterson, D., & Vacano, G. N. (2020). The CRISPR-Cas9 crA-TIC HeLa transcriptome: Characterization of a novel cellular model of ATIC deficiency and ZMP accumulation. *Molecular Genetics and Metabolism Reports*, *25*, 100642. https://doi.org/10.1016/j.ymgmr.2020.100642

Micheli, V., Camici, M., Tozzi, M. G., Ipata, P. L., Sestini, S., Bertelli, M., & Pompucci, G. (2011). Neurological disorders of purine and pyrimidine metabolism. *Current Topics in Medicinal Chemistry*, *11*(8), 923–947. https://doi.org/10.2174/156802611795347645

Ramond, F., Rio, M., Héron, B., Imbard, A., Marie, S., Billiemaz, K., Denommé-Pichon, A. S., Kuentz, P., Ceballos, I., Piraud, M., Vincent, M. F., & Touraine, R. (2020). AICA-ribosiduria due to ATIC deficiency: Delineation of the phenotype with three novel cases, and long-term update on the first case. *Journal of Inherited Metabolic Disease*, *43*(6), 1254–1264. https://doi.org/10.1002/jimd.12274

Sparrow, S. S., Cicchetti, D. V., & Balla, D. A. (2016). *Vineland adaptive behavior scales-II* (2nd ed.). Giunti Psychometrics.

Vincent, M. F., Bontemps, F., & Van den Berghe, G. (1992). Inhibition of glycolysis by 5-amino-4-imidazolecarboxamide riboside in isolated rat hepatocytes. *The Biochemical Journal*, *281*(Pt 1), 267–272. https://doi.org/10.1042/bj2810267

Wechsler, D. (2002). *Wechsler preschool and primary scale of intelligence: Technical and interpretative manual* (3rd ed.). The Psychological Corporation.
Wechsler, D. (2003). *Wechsler intelligence scale for children–fourth edition administration and scoring manual* (4th ed.). The Psychological Corporation.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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