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Clinical and Genetic Characterization of Two Colombian Patients with PURA-Related Neurodevelopmental Disorder: Expanding the Latin American Phenotypic Spectrum

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Case Report

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Abstract

PURA-related neurodevelopmental disorder (PURA-NDD) is a rare monogenic condition characterized by neonatal hypotonia, developmental delay, epilepsy, and variable multisystem involvement. Data from Latin America remains limited, limiting recognition of the disorder in underrepresented populations. We report two unrelated Colombian patients with neonatal onset hypotonia in whom routine metabolic studies, neuroimaging, and electrophysiological evaluation were initially non-diagnostic. Trio-based whole-exome sequencing identified de novo PURA variants in both individuals: a missense variant, c.221A > G (p.Tyr74Cys), affecting the PUR-I domain, and a truncating variant, c.733C > T (p.Arg245*), located in the PUR-III/C-terminal region. Although both patients shared profound hypotonia and global developmental impairment, their clinical trajectories differed. The first patient developed epilepsy, severe intellectual disability, autism spectrum disorder, and persistent motor incoordination without major respiratory compromise. The second patient showed marked feeding and respiratory involvement, including obstructive sleep apnea requiring nocturnal oxygen, but remained seizure-free at last follow-up. Comparison with previously reported Colombian and international cases further illustrates the broad phenotypic variability of PURA-NDD, even among variants affecting highly conserved functional domains. These observations expand the molecular and phenotypic spectrum of PURA-NDD in Latin America and support the early use of trio-based genomic testing in infants and children with unexplained neonatal hypotonia and developmental delay.

Introduction

Purine-rich element-binding protein A (PURA) encodes Pur-α, a highly conserved nucleic acid-binding protein that plays a central role in postnatal brain development, neuronal proliferation, dendritic maturation, and RNA trafficking [1]. Experimental and translational studies have shown that PURA is involved in multiple layers of gene regulation and cellular homeostasis, helping to explain why its disruption leads to a broad neurodevelopmental phenotype [1, 8].

In 2014, independent exome-based studies established de novo pathogenic variants in PURA as the cause of a recognizable neurodevelopmental disorder now broadly referred to as PURA-related neurodevelopmental disorder (PURA-NDD) [2, 3]. This spectrum includes individuals with heterozygous pathogenic sequence variants in PURA as well as patients with 5q31 microdeletions involving the gene [6, 7]. Since those first descriptions, the number of reported patients has grown steadily, and the phenotype has expanded well beyond the original presentation [4–7].

Clinically, PURA-NDD is most often characterized by neonatal or early infantile hypotonia, feeding difficulties, respiratory symptoms, and global developmental delay, followed by severe speech impairment and variable intellectual disability [4–7]. Epilepsy is common, but not universal, and additional manifestations may include abnormal movements, hypersomnolence, ophthalmologic abnormalities, dysmorphic features, gastrointestinal dysfunction, and other systemic complications [4–7]. This phenotypic expressiveness creates a substantial diagnostic challenge, particularly in infants whose initial metabolic, neuroimaging, or electrophysiological studies are unrevealing.

Despite increasing recognition of the disorder, robust genotype-phenotype correlations remain limited. Large cohort studies and more recent comparative analyses have consistently emphasized marked interindividual variability, including among patients harboring recurrent variants [4–6]. While some reports suggest that variant type or location may influence specific clinical tendencies, current evidence does not yet support deterministic predictions at the individual level [4–6, 8]. For this reason, careful description of additional patients remains clinically valuable, especially when they arise from populations that are still underrepresented in the literature.

Published experience from Latin America remains scarce, and regional documentation of PURA-NDD is still limited [9]. Expanding the clinical and molecular description of affected patients from this setting is relevant not only for phenotype delineation, but also for improving diagnostic recognition in health systems where access to genomic testing may be delayed or uneven.

Here, we report two unrelated Colombian patients with PURA-NDD carrying de novo variants in distinct functional regions of the protein. By placing these observations in the context of previously published reports, we aim to broaden the Latin American clinical and molecular spectrum of PURA-NDD and to underscore the value of early trio-based exome sequencing in children with unexplained neonatal hypotonia and developmental delay.

Case presentations

Patient 1

Patient 1 is a 22-year-old Colombian woman, the first child of healthy non-consanguineous parents, who presented in the neonatal period with profound axial and proximal hypotonia, hypoglycemia, and jaundice requiring an 8-day hospital admission. Initial investigations, including neurometabolic screening, brain magnetic resonance imaging, and a video-electroencephalogram, were unremarkable. Hypotonia was predominantly central, without clear clinical evidence of fatigability.

Her developmental course was markedly delayed. She achieved head control at 4 months, sat independently at 8 months, crawled at 18 months, and walked independently at 5 years of age. She never developed spoken language. During childhood, she developed severe intellectual disability and autism spectrum disorder. Epileptic seizures began in late infancy and have remained only partially controlled with carbamazepine and levetiracetam. At the most recent evaluation, she had a long myopathic facial appearance, a high-arched palate, a prominent nasal bridge, generalized hyporeflexia, and persistent motor incoordination. Her gait was broad-based and ataxic, with associated rocking movements and hand-flapping stereotypies.

Trio-based whole-exome sequencing identified a de novo heterozygous missense variant in PURA, c.221A > G (p.Tyr74Cys), classified as likely pathogenic. Management has focused on multidisciplinary neurodevelopmental follow-up, seizure control, physical therapy, and behavioral support.

Patient 2

Patient 2 is a 5-year-old girl, the second daughter of unrelated parents from rural area, born in a term after an uncomplicated pregnancy. Soon after birth, she developed respiratory distress, severe hypotonia, and feeding difficulties that required admission to the neonatal intensive care unit. Her developmental progress was profoundly delayed. Head control was achieved at 9 months and independent sitting at 24 months. At the most recent follow-up, she remained non-ambulatory and non-verbal, communicating through gestures and non-verbal vocalizations.

On examination, she had a broad forehead, epicanthal folds, a smooth philtrum, and a thin upper lip. She showed profound axial hypotonia with relative distal strength preservation, generalized hyporeflexia reduced reflexes, and intermittent dystonic posturing. Brain magnetic resonance imaging demonstrated mild frontal hypomyelination, whereas electroencephalography showed a normal background. Metabolic studies were unrevealing. Overnight polysomnography confirmed moderate obstructive sleep apnea, currently managed with nocturnal to maintain oxygen saturation > 94%.

Trio whole-exome sequencing identified a de novo heterozygous nonsense variant in PURA, c.733C > T (p.Arg245*), classified as pathogenic. Given her chronic respiratory vulnerability and the absence of clinical features suggestive of neuromuscular junction impairment, pyridostigmine was not trialed. Her current care remains supportive and includes respiratory monitoring, nutritional management, rehabilitation therapies, and developmental follow-up.

Although both patients shared the core features of PURA-related neurodevelopmental disorder, including severe hypotonia and global developmental impairment, their subsequent clinical trajectories differed substantially, particularly with respect to epilepsy and respiratory involvement.

Discussion

The two patients presented here reinforce the core clinical framework of PURA-related neurodevelopmental disorder (PURA-NDD)—namely neonatal hypotonia, feeding difficulties, severe developmental impairment, and long-term neurologic disability—while also illustrating the marked variability that continues to define this condition [4–7]. Although both individuals shared the expected early phenotype, their later clinical trajectories diverged substantially, particularly with respect to epilepsy, respiratory involvement, and motor manifestations. A notable strength of the present report is the comparison of two de novo variants affecting distinct regions of the PURA protein. Patient 1 carried the missense variant p.Tyr74Cys in the PUR-I region, whereas Patient 2 harbored the truncating variant p.Arg245* in the PUR-III/C-terminal region (Fig. 1). Together with the few Colombian patients published to date, these two cases broaden the national clinical and molecular spectrum of PURA-NDD. The main clinical and genetic features of the present patients and the previously reported Colombian cases are summarized in Table 1. A more detailed comparison of the Colombian cases and the published literature is provided in Online Resource 1 [4–6, 9, 12, 13].

Table 1
Clinical and genetic features of the present Colombian cases and previously reported Colombian patients with PURA-related neurodevelopmental disorder

Characteristic	Present case 1	Present case 2	López-Rivera et al. [7]	Mora-Martínez et al. [3]	Sinisterra-Díaz et al. [6]
Number of patients	1	1	1	1	1
Age at last evaluation	22 yr	5 yr	7 yr	7 yr	7 yr
Country	Colombia	Colombia	Colombia	Colombia	Colombia
Key craniofacial features	Long face, high-arched palate, prominent nasal bridge	Broad forehead, epicanthal folds, smooth philtrum, thin upper lip	Almond-shaped eyes, high hairline, flat philtrum	Flattened nasal bridge, thin upper lip	Almond-shaped eyes, high hairline, flat philtrum
Hypotonia	Severe	Severe	Severe	Severe	Severe
Developmental delay	Severe	Severe	Severe	Severe	Severe
Epilepsy	Present	Absent to date	Epileptiform abnormalities reported	Absent	Present
Feeding difficulties	Not reported	Present	Poor sucking ability, oropharyngeal dysphagia	Severe	Oropharyngeal dysphagia
Respiratory involvement	None	Sleep apnea requiring nocturnal oxygen	Hypopnea-apnea syndrome requiring CPAP	Severe respiratory involvement	Congenital pneumonia and aspiration
Other relevant features	Autism spectrum disorder, wide-based ataxic gait, stereotypies, scoliosis	Dystonic posturing, frontal hypomyelination, non-verbal, non-ambulant	Single palmar crease, flat feet	Vitiligo	Short stature, hirsutism, spasticity
PURA variant	c.221A > G	c.733C > T	c.697_699del	c.697_699del	c.692T > C
Predicted protein change	p.Tyr74Cys	p.Arg245*	p.Phe233del	p.Phe233del	p.Phe231Ser

Abbreviations: CPAP, continuous positive airway pressure; yr, years.

This table summarizes the main clinical manifestations and underlying PURA variants in the present Colombian patients and in previously published Colombian cases with molecularly confirmed PURA-related neurodevelopmental disorder.

The Colombian experience remains limited, but even within this small group, the phenotypic breadth is striking. The present cases, together with the previously reported national patients carrying p.Phe233del and p.Phe231Ser, show that the disorder may present through different clinical entry points, including epilepsy, feeding and respiratory compromise, neurobehavioral features, or abnormal motor development [9, 12, 13]. In this regard, Table 1 is particularly informative because it highlights both the shared core phenotype and the variability of associated manifestations across the Colombian cases, including epilepsy, sleep-disordered breathing, dystonic posturing, autism spectrum disorder, and distinctive craniofacial findings. This degree of heterogeneity is fully consistent with larger international cohorts, which have emphasized substantial interindividual variability, even among patients with recurrent variants [4–6].

From a clinical standpoint, the contrasting neurologic profiles of our two patients are relevant. Epilepsy has been reported in approximately half of individuals with PURA-NDD and may range from relatively limited seizure burden to developmental and epileptic encephalopathy [5, 6]. Patient 1 fits within this recognized epileptic spectrum, with early-onset seizures and persistent neurodevelopmental disability. By contrast, Patient 2 remained seizure-free at last follow-up but showed more prominent respiratory and feeding morbidity, including obstructive sleep apnea requiring nocturnal oxygen. This distinction is clinically important because it underscores that the absence of seizures does not imply a mild phenotype. Respiratory compromise may remain a major source of morbidity in PURA-NDD and deserve systematic monitoring, particularly in patients with severe hypotonia, feeding dysfunction, and sleep-related breathing abnormalities [4–7].

Motor findings also warrant attention. Patient 1 showed persistent stereotypies and motor incoordination, whereas Patient 2 had intermittent dystonic posturing. Although neither patient displayed the full mixed hyperkinetic phenotype described in recent video-based reports, their neurologic examination remains compatible with the expanding recognition of movement abnormalities within the PURA-NDD spectrum [10, 11]. Recent case series have shown that affected children may develop combinations of choreiform, dystonic, myoclonic, and stereotyped movements, sometimes leading to misclassification as dyskinetic cerebral palsy or other pediatric movement disorders [10, 11]. These observations are relevant for clinical practice because unusual movement patterns in a child with neonatal hypotonia and developmental delay should prompt consideration of a genomic diagnosis rather than a purely static encephalopathic label.

At the same time, our findings should be interpreted cautiously. Although some reports have suggested that variant class or protein location may influence certain clinical tendencies, currently available evidence still does not support deterministic genotype-phenotype rules for individual patients [4–7]. Large cohorts and comparative reviews continue to emphasize that PURA-NDD is a highly heterogeneous disorder and that recurrent variants may be associated with different levels of severity and distinct constellations of clinical manifestations [4–6]. Accordingly, the contrast between p.Tyr74Cys and p.Arg245* in our patients should be regarded as clinically informative and hypothesis-generating, but not as proof of a stable domain-specific predictive pattern. This distinction is important, particularly because previous work has also shown that PURA is a single-exon gene and that simple mechanistic assumptions based solely on variant class may be misleading [6].

Recent molecular studies offer a useful biological context for this phenotypic diversity. PURA is a structurally dynamic RNA- and DNA-binding protein, and pathogenic variants across the gene may disrupt folding, RNA binding, dimerization, or subcellular localization [1, 8]. Experimental work has shown that reduced PURA levels alter post-transcriptional regulation and impair P-body formation, while disease-causing variants can compromise PUR-domain integrity and weaken P-body association [8]. These mechanisms provide a plausible explanation for how variants affecting different regions of the protein can lead to a recognizable but clinically variable neurodevelopmental syndrome. Rather than supporting a single pathogenic route, the available data suggests that PURA dysfunction may converge on shared neurodevelopmental consequences through multiple molecular disturbances [1, 8].

From a therapeutic perspective, our cases reflect the current limits of precision treatment in PURA-NDD. Management remains largely supportive and multidisciplinary, focusing on seizure control, nutritional care, respiratory monitoring, rehabilitation, and developmental follow-up [4, 5, 7]. Anecdotal improvement with pyridostigmine or salbutamol has been described in a small number of patients with suspected neuromuscular junction involvement, but the evidence remains limited and heterogeneous [7]. Neither of our patients showed a convincing clinical picture of neuromuscular junction dysfunction, and in Patient 2, the burden of respiratory fragility further argued against an empirical cholinergic trial. For now, treatment decisions should remain phenotype-driven rather than genotype-driven.

This study has several limitations. It includes only two patients, and no functional assays were available to define the biological consequences of the identified variants in patient-derived material. In addition, comparison with literature must be interpreted cautiously because published cases vary considerably in age at last evaluation, depth of phenotyping, and completeness of longitudinal follow-up [4–6]. Nevertheless, these two Colombian patients add clinically well-characterized data from an underrepresented setting and reinforce a practical message for rare disease diagnosis: when neonatal hypotonia and developmental delay remain unexplained after standard investigations, early trio-based exome sequencing can substantially shorten the diagnostic odyssey and improve anticipatory care [4–6, 9, 12, 13].

Overall, these cases broaden the clinical and molecular spectrum of PURA-NDD in Latin America and support a phenotype-first but genomically informed approach to diagnosis and follow-up. Future progress will depend on larger harmonized cohorts, deeper functional studies, and prospective evaluation of neurologic, respiratory, and neuromuscular outcomes across the lifespan.

Conclusion

In conclusion, these two Colombian cases expand the clinical and molecular spectrum of PURA-related neurodevelopmental disorder in Latin America and further illustrate the marked phenotypic variability that characterizes this condition. Although both patients shared the core features of severe hypotonia and global developmental impairment, their subsequent courses differed substantially, particularly with respect to epilepsy and respiratory involvement. Rather than supporting rigid genotype-phenotype rules, these observations reinforce the need for careful, individualized clinical surveillance in patients with PURA-NDD. Our findings also highlight the diagnostic value of early trio-based exome sequencing in children with

unexplained neonatal hypotonia and developmental delay, especially when conventional investigations are unrevealing. Broader recognition of PURA-NDD in underrepresented regions will be essential to reduce the diagnostic odyssey, improve multidisciplinary care, and support future efforts toward more precise phenotype-informed management.

Declarations

Funding

No funds, grants, or other support were received for the submitted work.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

This study was approved for publication by the Institutional Research and Ethics Committee of the Faculty of Medicine, Pontificia Universidad Javeriana, and Hospital Universitario San Ignacio, Bogotá, Colombia, during the ordinary session held on December 12, 2024 (Minutes No. 22/2024; approval record FM-CIE-1461-24). The study was conducted in accordance with the ethical standards of the institutional and national research committee and with the Declaration of Helsinki and its later amendments.

Consent to Participate

Written informed consent to participate in this study was obtained from the legal guardians of both patients.

Consent for Publication

Written informed consent for publication of clinical data was obtained from the legal guardians of both patients. Identifying information has been omitted to protect patient privacy.

Data Availability

The datasets generated or analyzed during the current study are not publicly available because they include potentially identifiable clinical and genetic information from individual patients, but de-identified data may be made available by the corresponding author on reasonable request and subject to institutional and ethical restrictions.

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References

1. Molitor L, Bacher S, Burczyk S, Niessing D. The molecular function of PURA and its implications in neurological diseases. Front Genet. 2021;12:638217. https://doi.org/10.3389/fgene.2021.638217.
2. Hunt D, Leventer RJ, Simons C, Taft R, Swoboda KJ, Gawne-Cain M, et al. Whole exome sequencing in family trios reveals de novo mutations in PURA as a cause of severe neurodevelopmental delay and learning disability. J Med Genet. 2014;51(12):806–13. https://doi.org/10.1136/jmedgenet-2014-102798.
3. Lalani SR, Zhang J, Schaaf CP, Brown CW, Magoulas P, Tsai AC, et al. Mutations in PURA cause profound neonatal hypotonia, seizures, and encephalopathy in 5q31.3 microdeletion syndrome. Am J Hum Genet. 2014;95(5):579–83. https://doi.org/10.1016/j.ajhg.2014.09.014.
4. Reijnders MRF, Janowski R, Alvi M, Self JE, van Essen TJ, Vreeburg M, et al. PURA syndrome: clinical delineation and genotype-phenotype study in 32 individuals with review of published literature. J Med Genet. 2018;55(2):104–13. https://doi.org/10.1136/jmedgenet-2017-104946.
5. Johannesen KM, Gardella E, Gjerulfsen CE, Bayat A, Rouhl RPW, Reijnders M, et al. PURA-related developmental and epileptic encephalopathy: phenotypic and genotypic spectrum. Neurol Genet. 2021;7(6):e613. https://doi.org/10.1212/NXG.0000000000000613.
6. Dai W, Sun Y, Fan Y, Gao Y, Zhan Y, Wang L, et al. A 25 Mainland Chinese cohort of patients with PURA-related neurodevelopmental disorders: clinical delineation and genotype-phenotype correlations. Eur J Hum Genet. 2023;31(1):112–21. https://doi.org/10.1038/s41431-022-01217-4.
7. Mroczek M, Iyadurai S. Neuromuscular and neuromuscular junction manifestations of the PURA-NDD: a systematic review of the reported symptoms and potential treatment options. Int J Mol Sci. 2023;24(3):2260. https://doi.org/10.3390/ijms24032260.
8. Proske M, Janowski R, Bacher S, Kang HS, Monecke T, Koehler T, et al. PURA syndrome-causing mutations impair PUR-domain integrity and affect P-body association. eLife. 2024;13:RP93561.

https://doi.org/10.7554/eLife.93561.

9. Mora-Martinez S, Castaño-Giraldo N, Nati-Castillo HA, Barahona Machado L, Mora Arbeláez T, Gordillo-Gonzalez G, et al. Case report: Expanding the phenotypic spectrum of PURA syndrome in South America with the first presentation of concurrent vitiligo. Front Pediatr. 2024;12:1323014. https://doi.org/10.3389/fped.2024.1323014.
10. Crippa ACS, Bacheladenski EP, Rodrigues DCB, Ferreira LP, Meira AT, Franklin GL. Movement disorders in PURA syndrome: A video case series. Mov Disord Clin Pract. 2023;10(10):1542–6. https://doi.org/10.1002/mdc3.13804.
11. Franklin GL, Bacheladenski EP, Rodrigues DCB, Crippa ACS. Teaching Video NeuroImage: Stop-motion chorea in PURA syndrome. Neurology. 2023;100(10):492–3. https://doi.org/10.1212/WNL.0000000000201605.
12. Sinisterra-Díaz SE, Vasquez-Forero DM, Ordoñez L, Prieto LE, Pachajoa H. A Colombian boy with a novel de novo PURA variant: A case report. Mol Syndromol. 2024;1–5. https://doi.org/10.1159/000541654.
13. López-Rivera JJ, Rodríguez-Salazar L, Soto-Ospina A, Estrada-Serrato C, Serrano D, Chaparro-Solano HM, et al. Structural protein effects underpinning cognitive developmental delay of the PURA p.Phe233del mutation modelled by artificial intelligence and the hybrid quantum mechanics-molecular mechanics framework. Brain Sci. 2022;12(7):871. https://doi.org/10.3390/brainsci12070871.

Figures

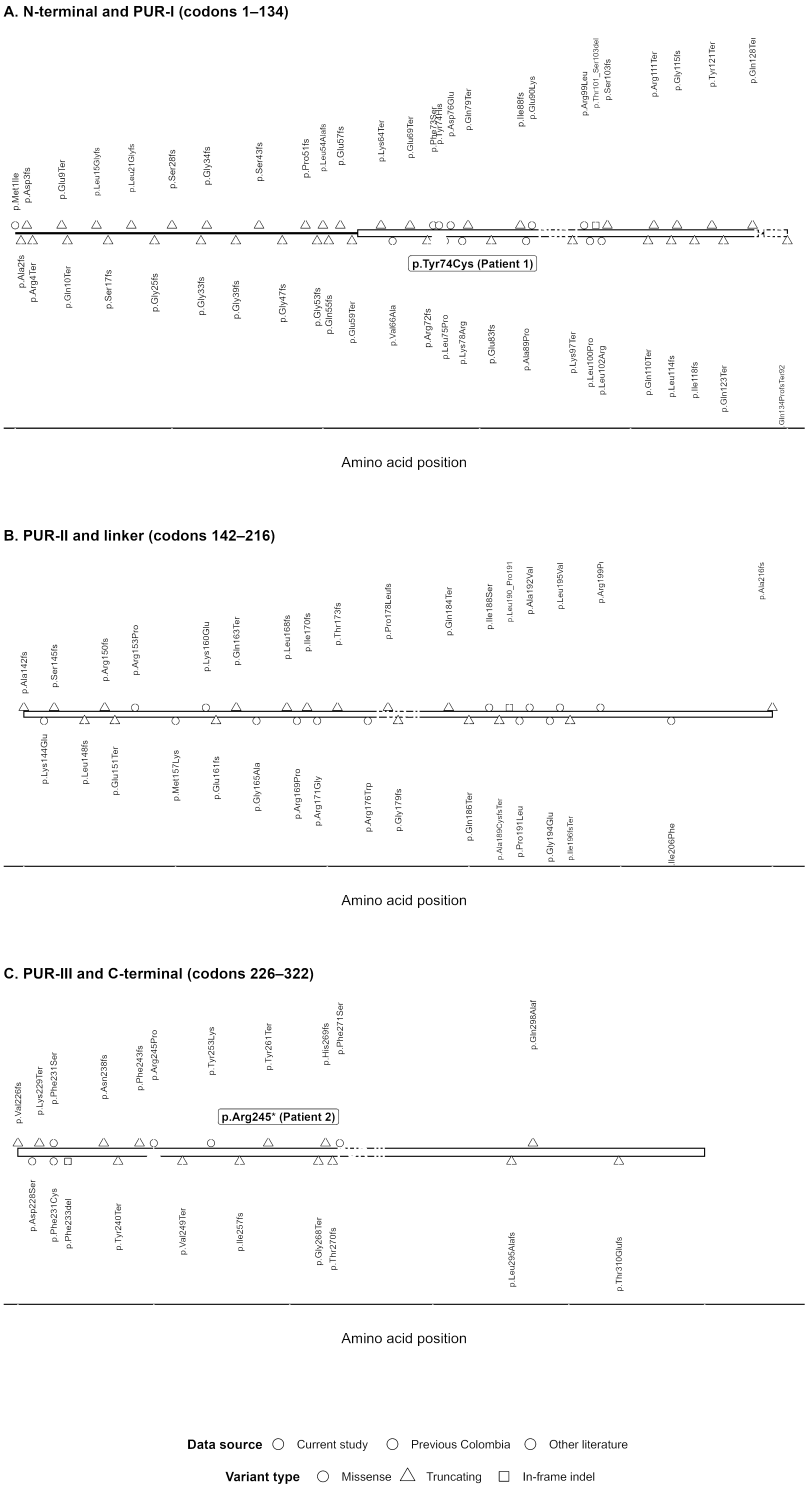


Figure 1

Distribution of reported PURA variants across the protein structure and location of the Colombian variants identified in the present series.

Figure legend. (A) N-terminal region and PUR-I domain (codons 1–134). (B) PUR-II domain and linker region (codons 142–216). (C) PUR-III domain and C-terminal region (codons 226–322). Variants identified in the

present study are highlighted alongside previously reported Colombian variants and variants collected from the published literature. Different symbols indicate variant class, including missense, truncating, and in-frame deletion variants. Patient 1 carried c.221A>G (p.Tyr74Cys) in the PUR-I region, whereas Patient 2 carried c.733C>T (p.Arg245*) in the PUR-III/C-terminal region

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTableS1PURA1.xlsx