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Clinical note

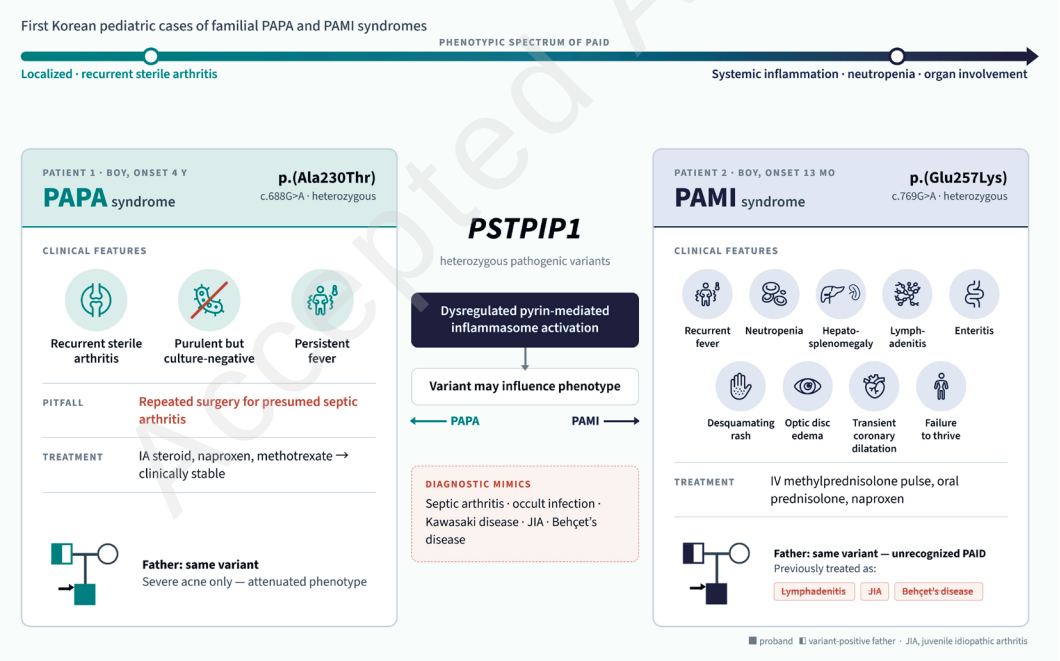
The expanding phenotypic spectrum of *PSTPIP1*-associated inflammatory diseases: first Korean pediatric cases of familial PAPA and PAMI syndromes

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PSTPIP1 (proline-serine-threonine phosphatase-interacting protein 1)-associated inflammatory diseases (PAID) encompass a spectrum of rare monogenic autoinflammatory disorders, most notably PAPA (pyogenic arthritis, pyoderma gangrenosum, and acne) syndrome and PAMI (*PSTPIP1*-associated myeloid-related proteinemia inflammatory) syndrome.[1] Both arise from *PSTPIP1* variants that dysregulate pyrin-mediated inflammasome activation, yet the specific variant may influence the resulting phenotype, ranging from isolated sterile arthritis to severe systemic inflammation. Because of their rarity and phenotypic heterogeneity, these conditions are frequently misdiagnosed, often leading to substantial diagnostic delay. We report 2 Korean children with genetically confirmed PAID and markedly different phenotypes.

Patient 1, a 7-year-old boy, presented with recurrent sterile arthritis and persistent fever that began at age 4, ultimately requiring 7 surgical interventions on the left



Graphic abstract. Phenotypic spectrum of *PSTPIP1*-associated inflammatory diseases (PAID) in 2 Korean children. Patient 1 had a heterozygous p.(Ala230Thr) variant and presented with PAPA syndrome. He had recurrent culture-negative purulent arthritis and underwent repeated surgery for presumed septic arthritis. Patient 2 had a heterozygous p.(Glu257Lys) variant and presented with PAMI syndrome, with recurrent fever, neutropenia, multiorgan involvement, and failure to thrive. In both families, the father carried the same variant with an attenuated or variable phenotype. IA, intra-articular; IV, intravenous; JIA, juvenile idiopathic arthritis; PAMI, *PSTPIP1*-associated myeloid-related proteinemia inflammatory; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; PSTPIP1, proline-serine-threonine phosphatase-interacting protein 1.

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knee, right hip, and left ankle for presumed septic arthritis. On examination, he had tenderness of the right elbow and a left-hand finger joint, restricted internal rotation of the left hip, and swelling with decreased dorsiflexion of the left ankle, without pyoderma gangrenosum, acne, or ocular abnormality. Synovial fluid was purulent in appearance yet consistently culture-negative across all 7 procedures. Inflammatory markers remained persistently elevated (C-reactive protein [CRP], 7.75 mg/dL; erythrocyte sedimentation rate [ESR], 44 mm/hr), and rheumatoid factor, HLA-B27, and autoantibody studies were negative. Bone scintigraphy showed increased uptake in the left lateral femoral condyle without other lesions (Fig. 1). Targeted next-generation sequencing (NGS) identified a heterozygous *PSTPIP1* variant (NM_003978.5:c.688G>A; p.(Ala230Thr)), classified as pathogenic according to the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) criteria, confirming PAPA syndrome.[2,3] He improved with intra-articular steroid, naproxen, and methotrexate, and has remained clinically stable over 10 months of outpatient follow-up. His father had longstanding severe acne and was found to carry the same variant on cascade testing.

Patient 2 presented at 13 months with an 11-day history of fever, diarrhea, cervical lymphadenitis, transient rash, enteritis, splenomegaly, and neutropenia (absolute neutrophil count [ANC], 400/μL), with elevated lactate dehydrogenase (456 U/L), ESR (70 mm/hr), and CRP (12.5 mg/dL); cultures were negative, and the fever resolved spontaneously. At 15 months, a second prolonged febrile episode (>10 days) again resolved without therapy, with similar laboratory findings (ANC, 700/μL) and persistently elevated inflammatory markers. Given recurrent fever of unknown origin and his father's history of lymphadenitis, juvenile idiopathic arthritis, and Behçet's disease, an autoinflammatory syndrome was suspected, and targeted NGS identified a heterozygous PSTPIP1 variant (NM_003978.5:c.769G>A; p.(Glu257Lys)), classified as pathogenic according to ACMG/AMP criteria, confirming PAMI syndrome.[4] Serum zinc and myeloid-related protein 8/14 (calprotectin) levels were not measured because they were not urgent, although measurement is being considered; the diagnosis was based on genetic confirmation and a compatible phenotype rather than the classical biomarker profile. Cascade testing confirmed that the father carried the same variant. At age 3, he developed a severe flare with fever, arthralgia, a desquamating rash, conjunctival injection, and optic disc edema. Laboratory tests showed elevated CRP (19.43 mg/dL), ESR (120 mm/hr), and serum amyloid A (>300 mg/L), with worsening neutropenia (ANC, 650/μL). Imaging confirmed hepatosplenomegaly, and echocardiography revealed isolated dilatation of the left anterior descending (LAD) coronary artery (diameter, 2.3 mm; *z* score 2.1). Intravenous methylprednisolone pulse therapy (30 mg/kg/day for 3 days; maximum, 1 g/day) resolved the fever, naproxen controlled the arthralgia, and the LAD dilatation resolved on echocardiography one week later. He has continued oral prednisolone and naproxen for 3 years since the flare (current age, 6 years), with height and weight persistently below the 1st percentile, indicating failure to thrive.

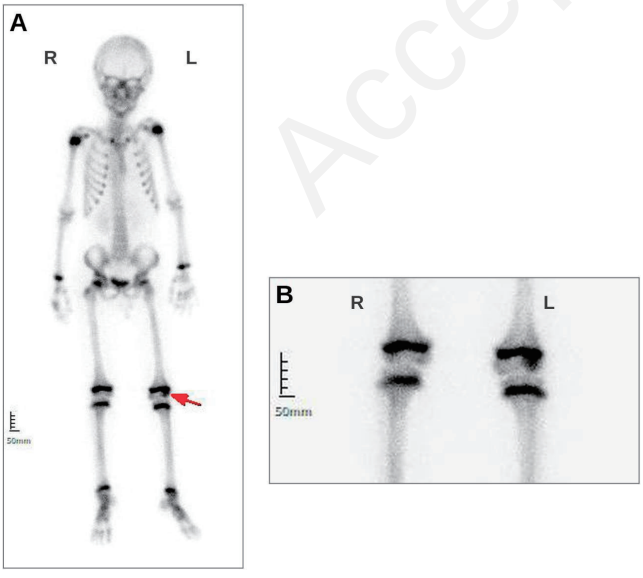


Fig. 1. Bone scintigraphy of patient 1 (anterior view). (A) Whole-body image showing increased uptake in the left lateral femoral condyle (arrow) without other focal lesions. (B) Magnified view of both knees. R, right; L, left.

Both patients' clinical and genetic features are summarized in Table 1. This phenotypic divergence may reflect the specific *PSTPIP1* variant involved.[1] Functionally, the charge-reversing p.(Glu250Lys) variant (PAMI) increases pyrin binding much more than the charge-neutralizing p.(Glu250Gln) variant (PAPA),[1] although this was not tested for p.(Ala230Thr) or p.(Glu257Lys) and cannot be directly extrapolated. PAPA syndrome typically presents with recurrent sterile arthritis and later cutaneous involvement.[2,3] Although Patient 1 has not developed pyoderma gangrenosum or acne, p.(Ala230Thr) has been reported with hidradenitis suppurativa, and one carrier remained asymptomatic until age 16 years;[5,6] his phenotype may therefore vary, and cutaneous features may emerge later. Purulent, culture-negative synovial fluid, as in patient 1, is a key feature distinguishing PAPA syndrome from septic arthritis.[7]

Both patients illustrate the diagnostic challenges of PAID: Patient 1 underwent 7 surgical interventions for presumed septic arthritis, and patient 2's fever, neutropenia, and splenomegaly could readily be attributed to infection. These findings echo frequent reports of misdiagnosis,[7,8]

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Table 1. Clinical and genetic profiles of the 2 patients with *PSTPIP1* variants

Variable	Patient 1 (PAPA syndrome)	Patient 2 (PAMI syndrome)
Sex	Male	Male
Age at diagnosis	7 Yr	15 Mo
Age at onset	4 Yr	13 Mo
Primary clinical features	Recurrent sterile arthritis, persistent fever	Recurrent fever, enteritis, lymphadenitis, hepatosplenomegaly
Cutaneous manifestations	None	Transient rash, desquamating rash
Laboratory and inflammatory findings	Elevated CRP, ESR	Elevated CRP, ESR, SAA, LDH; neutropenia
PSTPIP1 variant (NM_003978.5)	c.688G>A (p.(Ala230Thr))	c.769G>A (p.(Glu257Lys))
Family history	Father (severe acne; p.(Ala230Thr) carrier)	Father (p.(Glu257Lys) carrier; diagnosed with JIA and Behçet's disease)
Therapeutic interventions	Naproxen, methotrexate (ongoing), intra-articular steroid	IV methylprednisolone pulse, oral prednisolone (ongoing), naproxen (ongoing)

PSTPIP1, proline-serine-threonine phosphatase-interacting protein 1; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; PAMI, *PSTPIP1*-associated myeloid-related proteinemia inflammatory; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SAA, serum amyloid A; LDH, lactate dehydrogenase; NM_003978.5, NCBI RefSeq reference transcript for PSTPIP1; JIA, juvenile idiopathic arthritis; IV, intravenous.

supporting inclusion of PAID in the differential diagnosis of unexplained recurrent fever or sterile arthritis.

The family histories illustrate the variable expressivity of PAID.[5] A father–son pair carrying the same PAMI-associated variant has also been reported.[9] Each father carried the same variant as his child but had a milder or distinct phenotype, which may represent attenuated PAID rather than unrelated diagnoses. Because identical variants produced different phenotypes, and p.(Glu250Lys) has also been reported in PAPA patients,[5] modifier genes, environmental factors, or somatic mosaicism may contribute to phenotypic variability.

No consistently effective therapy has been established for PAMI syndrome,[1,4] and genotype–phenotype data have not yet guided treatment selection.[5] In a systematic review, improvement was reported in 8 of 14 patients treated with anti–tumor necrosis factor (TNF) agents and 6 of 15 treated with anti–interleukin-1 agents, although the evidence is limited to small case series.[4] Given patient 2's prolonged glucocorticoid exposure and persistent growth failure, anti-TNF therapy is being considered as a steroid-sparing option.

Although the coronary artery findings in patient 2 overlapped clinically with Kawasaki disease, the long-standing recurrent inflammation, neutropenia, and hepatosplenomegaly favored a PAMI-associated flare. This report has further limitations, including the small number of cases, the absence of biomarker measurements (serum zinc and calprotectin),[10] short follow-up, and single-center design.

These 2 cases demonstrate that PAID can present with diverse phenotypes, ranging from recurrent sterile arthritis to systemic inflammation, which may be influenced by the specific *PSTPIP1* variant. Genetic testing is essential for accurate diagnosis, and cascade family screening is recommended because affected relatives may show variable severity or be misdiagnosed.

Question

Which finding most strongly suggests a *PSTPIP1*-associated inflammatory disease in a child with recurrent arthritis?

(A) Positive synovial fluid culture
(B) Recurrent culture-negative purulent arthritis
(C) Isolated elevation of ESR
(D) Arthritis responding to antibiotics

Answer: B

Footnotes

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Author contribution: Conceptualization: SHK; Data curation: DL, YYC; Formal analysis: DL; Writing – original draft: DL; Writing – review & editing: SL; Project administration: SHK.

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