

## A novel *de novo* PSTPIP1 mutation in a boy with pyogenic arthritis, pyoderma gangrenosum, acne (PAPA) syndrome

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### ABSTRACT

*Autoinflammatory disorders are a group of Mendelian disorders characterised by seemingly unprovoked inflammatory bouts without high-titer autoantibodies or antigen-specific T-cells and are probably due to defects in the innate immunity. We here report on a 4-year-old Arabic boy with the clinical presentation of an autoinflammatory disorder, namely Pyogenic Arthritis, Pyoderma Gangrenosum and Acne (PAPA) syndrome. The presentation includes abscess formation after immunisation and recurrent mono-articular acute arthritis in various joints that responded favourably to systemic glucocorticosteroids, albeit without acne or pyoderma gangrenosum. The mutation analysis of the boy identified a novel de novo mutation in PSTPIP1, the gene responsible for PAPA syndrome. We recommend that the diagnosis of PAPA syndrome should be entertained in the differential diagnosis of patients with recurrent sterile pyogenic arthritis prior to the development of pyoderma gangrenosum or acne in order to initiate a timely management of the disorder.*

### Introduction

Autoinflammatory disorders are a group of illnesses characterised by attacks of seemingly unprovoked inflammation without significant levels of autoantibodies or antigen-specific T-Lymphocytes. The majority are Mendelian disorders and are thought to be due to abnormalities in the innate immune system (1). Pyogenic Arthritis, Pyoderma Gangrenosum and Acne (PAPA) syndrome (MIM 606347) is an autosomal dominant autoinflammatory disorder of skin and joints with clear evidence of involvement of IL-1 $\beta$  among other inflammatory pathways (2). PAPA syndrome was originally reported in 1997 in one large family with notable variable expression (3). However, it is believed that it was first described in 1975 in a report of a male patient with "streaking leukocyte factor", arthritis, and pyoderma gangrenosum (4). A second family was described as familial recurrent arthritis, also with variable expression (5). Thereafter, several families and sporadic cases were reported

marking the characteristic clinical features as early onset recurrent sterile pyogenic arthritis with prominent neutrophilic infiltrate. The skin manifestations are variable with ulceration or frank pyoderma gangrenosum; cystic acne, if present, became evident in adolescence (6).

Working on the two original families (3, 5), the responsible gene was mapped to the long arm of chromosome 15 (5, 7). The responsible gene was identified two years later by positional cloning as proline-serine-threonine phosphatase interacting protein 1 (*PSTPIP1*), also known as CD2 binding protein 1 (*CD2BP1*) (8). Two missense mutation in exons 10 and 11 of *PSTPIP1*, namely p.A230T and p.E250Q were reported in seemingly unrelated families and sporadic cases, suggesting a founder effect or a mutational hot spot (6). Two additional missense mutations in exon 11 were reported, namely p.E250K and p.D260N (2). Till now, 21 variants, not all have been deemed pathogenic, have been reported and maintained in a web-based mutation database for autoinflammatory disorders, which is being continually updated (<http://fmf.igh.cnrs.fr/ISSAID/infivers/search.php?n=5>) (9-11). Interestingly, several putative cases of PAPA syndrome have proven negative for *PSTPIP1* mutations (12).

We here report on an Arabic boy with clinical features suggestive of PAPA syndrome and a novel *de novo* missense mutation in exon 10 of *PSTPIP1* gene.

### Case report

A 45-month-old Jordanian male, born to healthy non-consanguineous parents, was evaluated for a past history of recurrent episodes of pyogenic arthritis, low-grade fever and acute arthritis of the right elbow joint, in Paediatric Rheumatology/Hamad General Hospital (HGH), Doha, Qatar for the first time. His initial evaluations were at Paediatric Immunology/Allergy/Rheumatology, Queen Rania Children Hospital, Amman, Jordan. Laboratory studies showed elevated acute phase reactants (ESR 97 mm/hr, CRP 128 mg/L, and ferritin 151  $\mu$ g/L), whereas blood cultures were negative. Magnetic

**Table I.** Chronological medical history.

Age	Clinical manifestations	Investigations	Treatment
6 months	Skin abscess at site of DPT vaccine	ESR ranged between 60–120 mm/hr. Soft tissue and bone biopsy and culture; inflammatory cells and negative cultures.	Intravenous antibiotics.
18 months	Skin abscess at site of DPT vaccine	ESR ranged between 60–120 mm/hr CRP between 62–128 mg/L.	Intravenous antibiotics (cloxacillin and vancomycin).
23 months	Acute right ankle arthritis. Low-grade fever for 3–4 days. Reduced activity.	Elevated acute phase reactants. Negative synovial fluid and blood cultures.	Intravenous antibiotics (cloxacillin and vancomycin). Surgical drainage.
24 months	Acute left wrist arthritis. Low-grade fever for 10 days. Reduced activity.	Elevated acute phase reactants. MRI: subcutaneous and deep soft tissue edema around the distal radius and ulna and the wrist joint. Mild effusion with rounded multiloculated cystic lesion in the deep soft tissue at the dorsum aspect of the distal ulna. Synovial fluid and blood cultures were negative. A synovial tissue biopsy: mixture of acute and chronic inflammatory infiltrate.	Intravenous antibiotics (cloxacillin and vancomycin). Surgical drainage.
26 months	Cellulitis of palmar aspect of his left hand close to site of surgical incision.	Elevated acute phase reactants.	Intravenous antibiotics.
27 months	Acute right wrist arthritis. Low-grade fever for 3–4 days. Reduced activity.	High WBC count, high Platelet count (513,000/mm <sup>3</sup> ). ESR 110 mm/hr and CRP 68 mg/L, and ferritin 47.5 µg/L (normal 6–24 µg/L) Normal IgG, IgA, IgM, and IgD. Negative synovial fluid and blood cultures.	Intravenous antibiotics (cloxacillin and vancomycin). Empiric colchicine 0.6 mg PO daily for 6 months.
27–42 months	Recurrent episodes of mono-articular arthritis left and right ankles.	None documented	Prednisone resulted in rapid resolution of symptoms.
42 months	Acute right elbow arthritis.	ESR 115 mm/hr and CRP between 62–128 mg/L. X-ray: soft tissue swelling	Oral prednisone tapered over 6 weeks.
45 months (described in the text)	Acute right elbow arthritis.	ESR 97 mm/hr, CRP 128 mg/L, and ferritin 151 µg/L. Negative blood cultures. Ultrasound: heterogeneous area of turbid fluid collection associated with subcutaneous edema. Whole body Tc-99 bone scan and gallium scan: inflammatory arthritis without osteomyelitis.	Intravenous cloxacillin then clindamycin for 10 days with Naproxen. Intravenous methylprednisolone started on day 11 with resolution within days. Oral prednisone tapered over 6 weeks
51 months	Left ankle arthritis while off prednisolone.	None available.	Prednisone 1 mg/kg/day.
58 months	Left ankle arthritis flare while tapering prednisone.	None available.	Increasing prednisone dose.
60 months	Left ankle arthritis flare while tapering prednisone.	None available.	Restarting naproxen 20 mg/kg/day.

DPT: diphtheria-pertussis-tetanus vaccine; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

resonance imaging (MRI) study showed features of arthritis, so intravenous antibiotics (cloxacillin then clindamycin) and naproxen (20 mg/kg/day) were started. After 10 days, there was only mild clinical improvement and a repeat MRI was unchanged. Antibiotics were discontinued and intravenous methylprednisolone was started at 1 mg/kg/day. Physical exam showed significant improvement within 48 hours and a tapering schedule of oral prednisone commenced 2 days later with complete resolution of clinical signs of arthritis.

Previous medical history and subsequent follow-up is summarised chronologically in Table I. The patient is normal between episodes with normal growth and development. There is no family history of similar conditions, and he has two older healthy sisters. Genetic testing for auto-inflammatory disorders was done at the age of four years at time of referral to HGH. Sequence analysis of the coding region of *PSTPIP1* and flanking intronic regions revealed two variations, c.657A>C, p.Gln219His (p.Q219H) and

c.736G>A, p.Asp246Asn (p.D246N). The first (p.Q219H) is present in the father who is completely asymptomatic, and was present in 4 out of 362 ethnically matched control chromosomes. It is reported as a SNP (rs139362350) with minor allele frequency of <0.01. The second (p.D246N) is a *de novo* variation in the child and absent in the parents and siblings, absent in 362 ethnically matched control chromosomes and predicted to be probably damaging by Polyphen-2 (<http://genetics.bwh.harvard.edu/pph2/>).

Follow-up visits showed recurrence of arthritis at the ages of 51, 58, and 60 months, as shown in Table I. Management thus far consisted mainly of oral prednisone and naproxen during disease flare. Anti-IL-1 agents such as anakinra or canakinumab are not available in Jordan and the family declined a trial of an anti-TNF biologic agent such as infliximab (13).

### Discussion

*PSTPIP1* is a cytoskeletal adaptor protein known to interact with PEST (rich in Proline - P, glutamic acid - E, serine - S and threonine - T residues) type protein phosphatase (PTP-PEST) (14, 15). The PAPA syndrome related mutations reported so far are in the coiled-coil region of *PSTPIP1*, which mediates PTP – PEST interaction, and it has been shown that p.A230T and p.E250Q variants abolish this interaction in yeast two-hybrid and co-immunoprecipitation experiments (1, 8, 16). It was also shown that pyrin (protein encoded by *MEFV* and implicated in familial Mediterranean fever), a cytoskeletal protein that modulates IL1 $\beta$  processing, NF $\kappa$ B activation and apoptosis, interacts with *PSTPIP1* and that p.A230T and p.E250Q variants markedly increase pyrin binding (16). Mutation analysis in our patient showed a novel variant, p.D246N, which is *de novo*, and is in the coiled-coil domain that harbors all the previously reported mutations. We anticipate that this mutation is the cause of the symptoms in this child, although we cannot predict the course of the disease.

PAPA syndrome typically presents in early childhood, with recurrent episodes of sterile, erosive arthritis occurring either spontaneously or after minor trauma. Oligo-articular pattern of arthritis involving non-axial joints is typical,

nonetheless, aggressive poly-articular disease have also been reported (17). Dermatological manifestations including debilitating aggressive skin ulcerations and cystic acne are also episodic but typically predominate after puberty. Although synovial fluid and skin lesions typically show features of inflammatory process, cultures from skin and joints are always sterile (3, 5, 17).

Our patient presented at a young age with recurrent episodes of mono-articular arthritis resembling septic arthritis. The recurrent episodes in different joints along with the clinical improvement when empiric courses of prednisone were used raised suspicion that a disease mechanism other than infection is operative. The detection of a putative mutation in the gene responsible for PAPA syndrome, *PSTPIP1*, confirmed the suspected diagnosis. We recommend that PAPA syndrome should be considered in the differential diagnosis of patients with recurrent sterile pyogenic arthritis even in the absence of cutaneous manifestations.

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