PSTPIP1 Gene Analysis in Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne (PAPA) Syndrome

Also known as: Familial Recurrent Arthritis (FRA); CD2-binding protein 1 (CD2BP1)

Mendelian Inheritance in Man Number: 604416 (PAPA syndrome); 606347 (PSTPIP1 gene)

Clinical features:
PAPA syndrome is an autoinflammatory disorder characterized by pyogenic sterile arthritis, pyoderma gangrenosum and acne. Patients exhibit early-onset inflammation of the joints, skin and muscle that is recurrent, destructive and occurs without discernible infection. Biopsies of synovial tissue show massive polymorphonuclear, neutrophil-rich infiltrates without the presence of immunoglobulin or complement deposits. The episodic inflammatory arthritis typically does not resolve spontaneously and must be treated with intra-articular steroids or surgical drainage of the infiltrate. Some affected individuals have expanding inflammatory, ulcerative skin lesions (pyoderma gangrenosum) and/or severe acne conglobata consisting of many painful abscesses and draining sinuses that heal with scarring. Pathergy, or injection site abscesses, are also common.

Inheritance pattern: Autosomal Dominant

Genetics:
PAPA syndrome is very rare and caused by mutations in the PSTPIP1 gene located on chromosome 15q24-q25.1. The gene product encoded by PSTPIP1 (Proline/Serine/Threonine phosphatase-interacting protein 1) is an adaptor protein known to interact with PEST-type protein tyrosine phosphatases (PTPs). It is thought to be involved in regulation of multiple cellular activities, such as cytoskeleton formation, apoptosis, stress response and T cell function. Mutations in the PSTPIP1 gene have been identified in several multi-generational families with PAPA syndrome and are hypothesized to result in dysfunction of the innate immune response, which causes perpetual low-level inflammation and spikes of trauma- or stress-induced accumulation of hyperactive inflammatory cells.

Reasons for referral:
1. Confirmation of a clinical diagnosis
2. Treatment decisions based on confirmation of diagnosis
3. Genetic counseling
4. Identification of at-risk family members
5. Prenatal diagnosis

Test methods:
Tier 1 testing consists of bi-directional sequence analysis of coding exons 10 and 11 and their corresponding splice sites, where all published mutations have been identified to date. If negative, tier 2 analysis of the remainder of the coding sequence and splice junctions (exons 1-9 and 12-15) of the PSTPIP1 gene is provided. Mutations found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, or another appropriate method.
Test Sensitivity and Mutation Spectrum
Two gain-of-function mutations, Ala230Thr and Glu250Gln, have been published in association with PAPA syndrome, both of which co-segregate with the disorder in multi-generational families.\(^1,2,3\) Two additional missense mutations, Glu250Lys and Asp266Asn, have also been identified in individuals with PAPA syndrome.\(^4\) Due to scarcity of scientific data, it is currently unknown what proportion of individuals with a clinical diagnosis of PAPA syndrome carry mutations in the PSTPIP1 gene. The methods used by GeneDx are expected to be >99% sensitive in detecting mutations in the PSTPIP1 gene that are identifiable by DNA sequencing, including the reported mutations.

Specimen Requirements and Shipping/Handling:
- **Blood:** A single tube with 1-5 mL whole blood in EDTA. Ship overnight at ambient temperature, using a cool pack in hot weather. Specimens may be refrigerated for up to 7 days prior to shipping.
- **Buccal Brushes:** As an alternative to blood, use a GeneDx buccal kit (others not accepted). Submit by mail. Buccal brushes are not accepted on children under 6 months of age.
- **Prenatal Diagnosis:** 10 mL amniotic fluid, 5 mg CVS, or 2 T25 flasks. Ship overnight at ambient temperature, using a cool pack in hot weather. Call to discuss requirements for parental blood. Keep backup cultures.

Required Forms:
- Sample Submission (Requisition) Form – complete all sides
- Payment Options Form or Institutional Billing Instructions

Prices and turn-around-time (fees are subject to change without notice):
- Test #2101: PSTPIP1 Mutation detection in a new patient (Tier 1) $500 Approx. 3-4 weeks
- Test #2102: PSTPIP1 Mutation detection in a new patient (Tier 2) $1190 Approx. 6-8 weeks
- Test # 901: DNA testing of a relative for a single known mutation* $350 Approx. 2-3 weeks
- Test # 902: Prenatal diagnosis for a known mutation* $2000 Approx. 2 weeks

* Please see our website for CPT codes/prices for carrier and prenatal testing: http://www.genedx.com.

CPT codes for mutation detection in a new patient (all codes and units apply):

<table>
<thead>
<tr>
<th>PSTPIP1 Tier 1 (exons 10 and 11)</th>
<th>PSTPIP1 Tier 2 (remaining exons)</th>
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</thead>
<tbody>
<tr>
<td>83891 x 5 units = $50</td>
<td>83891 x 7 units = $70</td>
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<tr>
<td>83898 x 5 units = $125</td>
<td>83898 x 14 units = $370</td>
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<tr>
<td>83894 x 5 units = $50</td>
<td>83894 x 14 units = $90</td>
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<td>83904 x 5 units = $175</td>
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<td>83892 x 2 units = $40</td>
<td>83892 x 2 units = $40</td>
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<tr>
<td>83912 x 2 units = $60</td>
<td>83912 x 2 units = $60</td>
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</table>

TOTAL $500 TOTAL $1190

ICD9 codes that might apply to new patients having this diagnostic test -
- 279.4 Periodic fever
- 706.1 Acne
- 686.01 Pyoderma gangrenosum

References: