



Hyper IgE Syndrome (HIES) Panel

Clinical Background

The hyper IgE syndrome (HIES) or Job's syndrome is a disorder of immunity and connective tissue. HIES is characterized by dermatitis, boils, cyst forming pneumonias, elevated serum IgE levels, retained primary dentition and bone abnormalities. HIES patients are highly vulnerable to extra-cellular bacteria and fungi such as *S. aureus* and *Candida albicans*, and develop recurrent skin and lung infections. Although the pattern of inheritance is chiefly autosomal dominant, sporadic cases may occur as well.

Transdominant mutations in the DNA binding or SH2 (Src homology 2 domains) of signal transducer and activator 3 (STAT3), as well as failure to generate IL-17 producing CD4⁺ T cells (TH17 cells) have been identified in HIES patients.

The Advanced Diagnostic Laboratories (ADx) at National Jewish Health offers genetic analysis of the DNA binding and SH2 domains of STAT3, as well as detection of TH17 cells for the evaluation of HIES patients.

HIES is frequently mistaken for atopic dermatitis, but patients with HIES are at a greater risk of serious infection than patients with atopic dermatitis

Clinical Utility:

HIES is frequently mistaken for atopic dermatitis, but patients with HIES are at a greater risk of serious infection than patients with atopic dermatitis. TH17 cells are known to be reduced in autosomal HIES syndrome caused by mutations in the STAT3 gene. The TH17 count can be used to aid in the differentiation between HIES and atopic dermatitis.

As the STAT3 form of HIES is transmitted in an autosomal dominant fashion, there is a 50% chance of passing the mutated gene on to offspring.

Evaluating for STAT3 deficiency will:

- Establish the diagnosis in suspected cases where overt facial dysmorphism may not be evident
- Help differentiate a known immunodeficiency from patients with severe atopy/eczema
- Provide prognostic information for patients and if positive, it generates anticipatory guidance for how to manage subsequent infections

Test Information:

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|--------------------------------|---|
| Test code: | STAT3 |
| Test name: | STAT3 SH2 and DNA Binding Sequence |
| Method: | PCR amplification followed by bi-directional sequencing of the DNA binding and SH2 domains |
| Reference range: | Normal |
| Specimen requirements: | 5 mL whole blood from a full green or lavender top tube. OR 2 buccal swabs |
| Transport requirements: | Blood: Send blood Priority Overnight via FedEx and in a well insulated container on an ice pack. Buccal Swab: Place swabs in sterile packaging, seal with tape, and ship samples in a padded envelope at room temperature. |
| Turn around time: | 4 weeks |
| CPT code: | 83891, 83898 x5, 83894 x5, 83892 x5, 83904 x5, 83912 |
| Note: | <i>Informed consent required prior to genetic testing completion. Forms can be downloaded from NJlabs.org</i> |

Test Information:

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|--------------------------------|--|
| Test code: | TH17 |
| Test name: | IL-17 producing CD4 T cells by flow cytometry |
| Method: | Lymphocyte stimulation followed by intra-cellular cytokine staining for IL-17 |
| Reference range: | By report |
| Specimen requirements: | 10 mL heparinized blood |
| Transport requirements: | 10 mL heparin whole blood (green top tube), room temperature, sample must be received in the lab within 24 hrs of draw |
| Turn around time: | 7 days |
| CPT code: | 86353, 88184, 88185 x 2 |

References:

1. Holland, S.M. et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med* **357**, 1608-1619 (2007).
2. Paulson, M.L., Freeman, A.F. & Holland, S.M. Hyper IgE syndrome: an update on clinical aspects and the role of signal transducer and activator of transcription 3. *Curr Opin Allergy Clin Immunol* **8**, 527-533 (2008).
3. Milner, J.D. et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature* **452**, 773-776 (2008).