

Hyper-IgE Syndromes (HIES) Panel

Clinical Features:

Hyper-IgE syndromes caused by pathogenic variants in the STAT3 and DOCK8 genes are characterized by eczema, sinopulmonary infections and greatly elevated serum IgE. Elevated IgE has also been observed in an individual with TYK2 deficiency and in individuals with Netherton syndrome, a disorder associated with variants in the SPINK5 gene.

STAT3 (Autosomal Dominant HIES): Patients with AD-HIES have lifelong eczema, eosinophilia, and recurrent staphylococcal skin abscesses (recalling the infliction of the biblical character Job). The abscesses are “cold”, i.e. with remarkably little inflammatory response. Serum IgE levels are characteristically at least 10-fold elevated. Patients are prone to cyst-forming pneumonia (typically staph, hemophilus or pneumococcus) and mucocutaneous candidiasis. The face may be coarse and asymmetric. Non-traumatic fractures and scoliosis are typical, and dental deciduation is delayed. Other features reported include hyperextensibility, coronary artery aneurysms, brain lesions, craniosynostosis, and Chiari malformations. Individuals with AD-HIES are also at an increased risk for malignancies, particularly lymphomas.

DOCK8 Immunodeficiency Syndrome (DIDS): DIDS is similar to AD-HIES, but without the skeletal, dental and connective tissue findings. It can also be distinguished from AD-HIES by the increased number of cutaneous viral infections and the higher prevalence of severe allergies. In addition, although both AD-HIES and DIDS are associated with increased risk of sinopulmonary infections, AD-HIES infections are commonly due to *S. aureus*, while DIDS infections are more varied. Malignancies are more common with DIDS, with lymphomas and squamous cell carcinomas the most prevalent.

TYK2 Deficiency: To our knowledge, only two patients have been reported with TYK2 pathogenic variants. Both patients had sinopulmonary infections, BCG infections and cutaneous viral infections; however, only one patient had elevated IgE and skin abscesses.^{6,7}

Netherton Syndrome (NTS): Netherton syndrome (NTS) is a congenital disorder of the skin, hair and the immune system. NTS usually manifests at birth with generalized redness and scaling of the skin resembling non-bullous congenital ichthyosiform erythroderma (NCIE) or, rarely, with a collodion membrane. Generalized erythema and scaling may either persist lifelong, or develop into itchy, scaling plaques called “ichthyosis linearis circumflexa”. Associated are hair shaft abnormalities, in particular “bamboo hair” also known as “trichorrhexis invaginata”, which may lead to diffuse alopecia of the scalp and loss of eyebrows and eyelashes. Most patients have highly elevated serum levels of immunoglobulin E and

various allergies. In severe cases, failure to thrive, growth retardation, and immune defects resulting in serious recurrent infections may complicate NTS.

Test Methods:

Using genomic DNA obtained from a blood specimen (2-5 mL in EDTA), all coding exons of 4 genes (DOCK8, SPINK5, STAT3, SPINK5) including their splice junctions, are sequenced using a state-of-the-art solid-state sequencing-by-synthesis process that allows sequencing of a large number of amplicons in parallel.⁸ For analysis, DNA sequence of the coding exons is assembled and compared to the published genomic reference sequences. In addition, deletion/duplication analysis of the DOCK8 gene by targeted array CGH analysis with exon-level resolution is included. The presence of any variants or potentially disease-associated sequence variants is confirmed by conventional dideoxy-DNA sequence analysis or another appropriate method. Previously offered single gene sequencing of the STAT3 gene and deletion/duplication analysis of the DOCK8 remains available. In addition, sequencing of the DOCK8 gene or sequencing and deletion/duplication analysis of the DOCK8 gene as stand-alone tests are now available.

Test Sensitivity and Genetics:

Gene	Sensitivity	Inheritance	Variant Spectrum
<i>STAT3</i>	~60% ⁴ of individuals with suspected AD-HIES harbor STAT3 variants	Autosomal Dominant	Single base-pair substitutions, small insertions/deletions, large deletions (<<1%)* The majority of variants are located in exons 13-16, 20 and 21. ^{12,13}
<i>DOCK8</i>	~75% ⁵ of individuals with a suspected recessive form of HIES harbor DOCK8 variants	Autosomal Recessive	Large deletions, single base-pair substitutions, small deletions
<i>SPINK5</i>	~66-75% of individuals with suspected NS harbor SPINK5 variants ⁹	Autosomal Recessive	Single-base pair substitutions (nonsense, splice-site), small insertions/deletions, large deletions (<<1%)*
<i>TYK2</i>	<<1% ⁶	Autosomal Recessive	Small deletions

* Heterozygous deletions of one or more exons in any gene other than DOCK8 would not be detected by this analysis. To date, to our knowledge, a large deletion involving the STAT3 gene has been observed in only one individual and a large deletion involving the SPINK5 gene has only been observed in a single family.^{4,10}

References:

1. Freeman et al., (2010) *Disease Markers*. 29:123-130.
2. Zhang et al., (2011) *Curr Opin Pediatr*. 23(6):653-658.
3. Szczawinska-Poplonyk et al., (2011) *Orphanet Journal of Rare Diseases*. 6:76.
4. Schimke et al., (2010) *J Allergy Clin Immunol*. 126(3):611-617.
5. Engelhardt et al., (2009) *J Allergy Clin Immunol* 124:1289-1302.
6. Minegishi et al., (2006) *Immunity*. 25(5):745-755.
7. Kilic et al., (2012) *J Pediatr*. 160(6):1055-1057.
8. Bennett S. (2004) *Pharmacogenomics*. 5(4):433-8.
9. Richard et al., (2004) *J Invest Dermatol*. 122:483A.
10. Hachem et al., (2006) *J Invest Dermatol*. 126:1609-1621.
11. Minegishi et al., (2007) *Nature* 448:1058-1062.
12. Holland et al., (2007) *NEJM*. 357:1608-1619.