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:**
Genomic DNA is extracted from the submitted specimen. For skin punch biopsies, fibroblasts are cultured and used for DNA extraction. The DNA is enriched for the complete coding regions and splice site junctions of the genes on this panel using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to reference sequences based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons at the exon-level; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. For the SPINK5, STAT3, and TYK2 genes, sequencing but not deletion/duplication analysis is performed. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

**Technical Test Sensitivity:**
The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events, but less for deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test identify most deletions and duplications involving coding exons but are less reliable for detecting copy number variants of less than 500 base pairs. Assessment of copy number events also depends on the inherent sequence properties of the targeted regions, including shared homology and exon size. Mosaicism detection is limited and balanced chromosome aberrations cannot be identified.
### Sensitivity and Genetics:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sensitivity</th>
<th>Inheritance</th>
<th>Variant Spectrum</th>
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<tbody>
<tr>
<td>STAT3</td>
<td>~60%</td>
<td>Autosomal Dominant</td>
<td>Single base-pair substitutions, small insertions/deletions, large deletions (&lt;&lt;1%)*</td>
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<tr>
<td></td>
<td>of individuals with suspected AD-HIES harbor STAT3 variants</td>
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<td>The majority of variants are located in exons 13-16, 20 and 21.12,13</td>
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<tr>
<td>DOCK8</td>
<td>~75%</td>
<td>Autosomal Recessive</td>
<td>Large deletions, single base-pair substitutions, small deletions</td>
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<td></td>
<td>of individuals with a suspected recessive form of HIES harbor DOCK8 variants</td>
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<tr>
<td>SPINK5</td>
<td>~66-75%</td>
<td>Autosomal Recessive</td>
<td>Single-base pair substitutions (nonsense, splice-site), small insertions/deletions, large deletions (&lt;&lt;1%)*</td>
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<tr>
<td></td>
<td>of individuals with suspected NS harbor SPINK5 variants9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TYK2</td>
<td>&lt;&lt;1%</td>
<td>Autosomal Recessive</td>
<td>Small deletions</td>
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* 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: