Hyper-IgM Panel

**Disorder also known as:** Type 1: X-linked Hyper-IgM Immunodeficiency, Hyper-IgM Syndrome Type 1; Type 2: Hyper-IgM Syndrome Type 2; Type 3: Hyper-IgM Syndrome Type 3; Type 5: Hyper-IgM Syndrome Type 5

**Panel Gene List:** CD40LG, AICDA, CD40, UNG

**Clinical Features:**
In all forms of Hyper-IgM (HIGM) syndrome, the normal process of immunoglobulin heavy chain class switching from IgM to other classes fails. Patients have low to absent serum IgG, IgA and IgE with normal to elevated levels of IgM. Hyper-IgM syndrome Type 1, caused by variants in the CD40LG gene, is by far the most common type, accounting for approximately 65-70% of HIGM cases. Type 2 (caused by variants in AICDA) accounts for likely less than 5% of cases, while Type 3 (caused by variants in CD40) and Type 5 (caused by variants in UNG) account for only a small number of cases.\(^4,5\)

Hyper-IgM syndrome Types 1 and 3 are clinical similar, with patients displaying a more severe phenotype compared to Types 2 and 5. These individuals often present with severe, recurrent sinopulmonary infections, Pneumocystis jeroveci (aka Pneumocystis carinii) pneumonia (PCP), chronic diarrhea and may have intermittent or persistent neutropenia.\(^4,5\) A distinguishing feature of Types 1 and 3 is that individuals are susceptible to opportunistic infections, which is typically not observed in individuals with Types 2 or 5. In addition, individuals with Types 1 or 3 often present at an earlier age (within the first one or two years of life) as compared to individuals with Types 2 or 5, where age of onset can vary from as early as the first few years of life to even as late as the second decade.

Hyper-IgM syndrome Types 2 and 5 are also clinically similar. These individuals typically have a milder disease presentation; the most common features observed are a susceptibility to bacterial infections and lymphoid hyperplasia. One important biochemical difference between these two types is that individuals with Type 5 have normal rates of somatic hypermutation (SHM), while individuals with Type 2 typically do not have intact SHM (although variants in a specific region of the AICDA gene can result in normal SHM frequencies).\(^6\)

**Test Methods:**
Using genomic DNA from the submitted specimen, the complete coding regions and splice site junctions of the genes on this panel are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNVCNV). 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. Alternative sequencing or copy number detection methods are used to analyze regions with inadequate sequence or copy number data. 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.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect 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 cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations. Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

**Test Sensitivity:**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Protein</th>
<th>Inheritance</th>
<th>Disease Associations</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD40LG</td>
<td>CD40 ligand</td>
<td>XL</td>
<td>Hyper-IgM</td>
<td>67%4</td>
</tr>
<tr>
<td>AICDA</td>
<td>Activation-induced cytidine deaminase</td>
<td>AR; AD - R190X</td>
<td>Hyper-IgM</td>
<td>~3.5%4</td>
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<tr>
<td>CD40</td>
<td>CD40 molecule</td>
<td>AR</td>
<td>Hyper-IgM</td>
<td>Rare7,8,9</td>
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<tr>
<td>UNG</td>
<td>Uracil DNA glycosylase</td>
<td>AR</td>
<td>Hyper-IgM</td>
<td>Rare10,11</td>
</tr>
</tbody>
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**References:**