CD40LG, AICDA, CD40 and UNG Gene Analysis in Immunodeficiency Syndrome with Hyper-IgM (Types 1, 2, 3 and 5)

**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 jiroveci (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).\(^6\)

**Genetics:**
Type 1 (CD40LG) is inherited in an X-linked manner whereas Types 2 (AICDA), 3 (CD40), and 5 (UNG) are inherited in an autosomal recessive manner. A single common sporadic variant in the AICDA gene (R190X) acts in a dominant manner.
A variety of variants have been identified in the CD40LG, with the vast majority comprising missense, nonsense and splice site variants, as well as small deletions and insertions. Large deletions and a single insertion of this gene have also been observed.\textsuperscript{4,14} A variant in the promoter region and one possible variant located deep within an intron have been observed in one family each, indicating that these are likely very rare variants.\textsuperscript{12,13}

A variety of missense, nonsense, small insertions or deletions, and splice variants have been described throughout the AICDA gene, as well as partial and whole gene deletions.\textsuperscript{1,2,3} The stop variant R190X is notable for dominant inheritance.\textsuperscript{2,3}

Variants that have been identified in the CD40 gene in association with Hyper-IgM syndrome include missense changes, splice site alterations, and a single small deletion.\textsuperscript{7,8}

All currently known variants in the UNG gene have been identified in the catalytic domain – these include small deletions and missense changes.\textsuperscript{10,11}

**Test Methods:**

Analysis is performed by bi-directional sequencing of the coding regions and splice sites of the CD40LG (exons 1-5), AICDA (exons 1-5), CD40 (exons 1-9) and UNG (exons 1-7) genes. If sequencing identifies a single variant on one allele of the AICDA gene or one allele of the CD40LG gene in an affected female, targeted array CGH analysis with exon-level resolution (ExonArrayDx) will be performed to evaluate for a deletion or duplication of one or more exons of this gene at no additional charge. Variants 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:**

In a large cohort study of 115 families where at least one family member was diagnosed with Hyper-IgM syndrome, a causative variant was identified in approximately 75% of families.\textsuperscript{4} The vast majority of variants were identified in the CD40LG gene, accounting for over 65% (77/115) of all identified variants. Variants in the AICDA gene were observed in 4/115 families (~3.5%). These AICDA positive cases represented approximately 10% of the families where a CD40LG variant had already been ruled out. Variants in the CD40 and UNG genes are very rare, and have only been identified in a small number of case studies.\textsuperscript{7,8,9,10,11} Almost all known variants in the AICDA, CD40LG, CD40 and UNG genes would be expected to be identified by this analysis. Variants present in the regulatory regions or deep within an intron would not be identified; however, these types of variants appear to be very rare, with only one family reported to harbor a variant in the promoter region of the CD40LG gene\textsuperscript{12} and possibly one variant identified deep with an intron of this gene in another family.\textsuperscript{13}
References: