

IRAK4 Deficiency

Disorder also known as: Predisposition to Pyogenic Infections; Invasive Pneumococcal Disease

Clinical Features:

Children with recurring and often invasive infections with *Streptococcus pneumoniae*, *Staphylococcus aureus* and other pyogenic bacteria can be suspected of having a congenital deficiency in IRAK4, an intracellular kinase associated with Toll-Like Receptor and Interleukin-1 Receptor pathways.¹ Febrile response is reduced and failure of leukocyte response to bacterial endotoxin and Interleukin 1 can be demonstrated in vitro. Leukocyte counts are normal. Infections can be peripheral (e.g. tonsillitis, otitis media) or invasive (e.g. meningitis, arthritis, abdominal abscess) and may be life-threatening. In surviving patients the susceptibility decreases with age and the risk of invasive infections appears to disappear by adolescence or adulthood.

Inheritance Pattern:

Autosomal recessive

Test Sensitivity:

IRAK4 gene variants are suspected in primary immunodeficiency where the susceptibility is strictly limited to pyogenic extracellular bacteria. The percent of such patients who have IRAK4 deficiency is thought to be high, but other genes including the X-linked gene NEMO3 could account for some cases. If two IRAK4 variants are present in a patient, this test is 98% likely to detect one, if not both variants.

Variant Spectrum:

In the initial summary² of the first 18 independent patients, 35 of 36 variants were frameshift, splice site, or nonsense variants or deletions of one or more exon, all of which would be detectable by the strategy used. The reported deletions were of exons 1, 9, or the whole gene, and were seen in 1 family each. Importantly, the nonsense variant Q293X was found in 10 of 18 of the initially reported families where it accounts for 17 of the initial 36 variants seen. Lastly, one of the 36 alleles contained a deep intronic variant, which would not be detected by this study.

Test Methods:

Using genomic DNA from the submitted specimen, the coding regions and splice junctions of the requested gene are PCR amplified and capillary sequencing is performed. Bi-directional sequence is assembled, aligned to reference gene sequences based on NCBI RefSeq

transcript and human genome build GRCh37/UCSC hg19, and analyzed for sequence variants. Concurrent deletion/duplication testing is performed for most, if not all, of the coding exons using exon-level oligo array CGH (ExonArrayDx), and data analysis is performed using gene-specific filtering. Probe sequences and locations are based on human genome build GRCh37/UCSC hg19. Reported clinically significant variants are confirmed by an appropriate method. Sequence and copy number variants are reported according to the Human Genome Variation Society (HGVS) or International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively. 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.

References:

1. Picard et al. (2003) *Science* (New York, N.Y.) 299 (5615):2076-9 (PMID: 12637671)
2. Ku et al. (2007) *The Journal Of Experimental Medicine* 204 (10):2407-22 (PMID: 17893200)
3. Ku et al. (2007) *Journal Of Medical Genetics* 44 (1):16-23 (PMID: 16950813)