

## BTK Gene Analysis in X-linked Agammaglobulinemia (XLA)

### DISORDER ALSO KNOWN AS

Bruton type agammaglobulinemia; XLA; congenital hypogammaglobulinemia.

### CLINICAL FEATURES

Affected individuals are males who have an increased susceptibility to bacterial infections due to severely reduced immunoglobulins of all isotypes. The underlying cause of XLA is an arrest of B-cell differentiation, which leads to an extreme deficiency of mature B lymphocytes (<1% of the normal value) and an absence of plasma cells. The age of onset of infections is generally around 6-12 months, with the average age of diagnosis at 3 years. Infections originating in mucosal surfaces are common in patients with XLA, and they may progress to the blood or other organs if left untreated. Pneumonia, meningitis, septic arthritis, cellulitis and septicemia can be seen in patients with XLA. Affected individuals may have an increased risk of colorectal cancer. Treatment entails immunoglobulin replacement and antibiotics. Female carriers are usually asymptomatic and have skewed X inactivation in B cells corresponding to expansion of only those B cells that use the normal BTK allele.

### INHERITANCE PATTERN/GENETICS

X-linked recessive

### TEST METHODS

Analysis is performed by bi-directional sequencing of the coding regions and splice sites of exons 2-19 of the BTK gene, as well as the non-coding exon 1. In addition, patients are tested concurrently by targeted array CGH analysis with exon-level resolution (ExonArrayDx) in order to detect duplications and deletions. 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

About 85% of patients with defects in B cell development have XLA, for which BTK is the only known mutated gene.<sup>1</sup> Sequencing can detect about 93% of BTK variants in males and about 90% in females, while the inclusion of array-based all-exon copy number analysis brings the sensitivity to about 97% for both.

Loss-of-function variants occur throughout the coding sequence of the gene and include nonsense, missense, splice-site, deletions and insertions.<sup>2</sup> 60-70% of variants are point variants, 20-30% of variants are small deletions or insertions detectable by sequencing, and 10% are large deletions, duplications, inversions and insertions.<sup>1</sup>

### REFERENCES:

1. Conley ME et al, 2005, Genetic analysis of patients with defects in early B-cell development, Immunological Reviews 203:216.

2. Mutations of the human BTK gene coding for Bruton tyrosine Kinase in X-linked agammaglobulinemia, 1999, Vihinen, M et al, Human Mutation 13:280-285.