

# Interleukin-1-Receptor-Associated Kinase-4 Deficiency Screen

*SCREENS FOR DEFECTIVE INNATE IMMUNITY IN PATIENTS WITH RECURRENT INFECTIONS IN WHOM OTHER IMMUNODEFICIENCIES HAVE BEEN EXCLUDED*

## Test Highlights

- Screens for IRAK-4 deficiencies in patients with recurrent infections and poor inflammatory responses.
- A small amount of whole blood is stimulated with lipopolysaccharide (LPS) and zymosan particles, followed by measurement of the inflammatory monokines TNF $\alpha$ , IL-1 $\beta$ , and IL-6 by Luminex multianalyte technology.
- A lack of response to these stimuli can indicate an IRAK-4 deficiency and provide valuable information to the clinician.

## Clinical Background

- Some patients with recurrent pyogenic bacterial infections have been shown to have IRAK-4 deficiencies. Some of the organisms involved include *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Shigella sonnei*.
- These patients usually have normal serum antibody titers against protein and polysaccharide antigens, normal immunoglobulins, complement concentrations, neutrophil function, and normal T and B cells.

## Disease Overview

IL-1-receptor-associated kinase-4 (IRAK-4) deficiency is associated with a narrow cellular defect first described in three patients with histories of recurrent infections caused by gram-positive organisms, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. This defect results from a lack of response of toll-like receptor (TLR) ligands and IL-1 receptors (IL1Rs), which have been shown to bind microbial products and initiate an immune response stimulating the inflammatory monokines, TNF $\alpha$ , IL-1 $\beta$ , and IL-6, which can then amplify the immune response. Cells of these patients fail to produce these cytokines in response to lipopolysaccharide (LPS) and zymosan particles. This lack of response can provide the clinician with more data in order to help establish a diagnosis.

## Indications for Ordering

Patients with recurrent bacterial infections and poor inflammatory responses due to pyogenic bacteria in whom all other immunodeficiencies have been excluded.

## Interpretation

Abnormal results suggest possible IRAK-4 deficiency.

## Limitations

This assay should be considered a screening test only. The clinician should take into consideration the clinical status of the patient when ordering and interpreting the data.

## Methodology

- Cell stimulation of a whole blood sample in tissue culture followed by measurement of monokine production in supernatant by Luminex multianalyte technology.
- All values will be compared to the whole blood sample incubated with media alone, which is usually less than 5 pg/mL for all three monokines tested. Any values above this level should be considered normal and patient values less than 5 pg/mL below normal. The medical director determines whether there is a depressed response to the stimulants tested, indicating a possible IRAK-4 deficiency.

## References

1. Chapel H, et al. *Shigella sonnei* meningitis due to interleukin-1 receptor-associated kinase-4 deficiency: first association with a primary immune deficiency. *Clin Infect Dis* 2005;40:1227-31.
2. Lye E, et al. The role of interleukin 1 receptor-associated kinase-4 (IRAK-4) kinase activity in IRAK-4-mediated signaling. *J Biol Chem* 2004;279:40653-8.
3. Orange JS. Congenital immunodeficiencies and sepsis. *Pediatr Crit Care Med* 2005;6:S99-S107.
4. Picard C, et al. Pyogenic bacterial infections in humans with IRAK-4 deficiency. *Science* 2003;299:2076-9.
5. Suzuki N, et al. A critical role for the innate immune signaling molecule IRAK-4 in T cell activation. *Science* 2006;311:1927-32.

## Test Information

**0051393**      **Interleukin-1-Receptor-Associated Kinase-4 (IRAK-4) Deficiency Screen**

For specific collection, transport, and testing information, refer to the ARUP Web site at [www.aruplab.com](http://www.aruplab.com).

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at [www.arupconsult.com](http://www.arupconsult.com).