

# Genes-4U

## Toll-like receptor 4 (TLR4) Asp299Gly (A896G) and Thr399Ile

The two cosegregating missense mutations Asp299Gly (A896G) and Thr399Ile in the human Toll-like receptor 4 (TLR4 \*) gene have recently been discovered and occur with an allele frequency between 3.3 and 7.9 %. The mutations were shown to be associated with hyporesponsiveness to inhaled endotoxin in humans in vivo (1). This finding was recently replicated. In addition, these authors showed by transfection of THP-1 cells that the **Asp299Gly mutation** but not the Thr399Ile mutation **interrupts TLR4-mediated LPS signaling** (2).

It is likely that these relatively common variants also influence the response to endotoxin and gram-negative infection in other clinical settings.

Studies in mice recently revealed that animals with non-functional TLR4 (C3H/HeJ mice) showed significantly less alcohol-induced liver injury (3), **implicating** bacterial LPS and **the functionality of TLR4** on Kupffer cells and the ensuing production of TNF alpha **in alcohol-induced damage**. Also, C3H/HeJ mice showed **drastically reduced Ozone-induced lung hyperpermeability** in comparison with C3H/OuJ mice from which they differ only by the non-functional TLR4 gene (4). Studies on the role of TLR4 mutations in human alcohol – and Ozone – induced pathology are likely to follow soon.

### References

\* GenBank accession numbers for TLR4 : U93091, U88880 and AF057025

1. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Arbour N.C. et al. Nature Genetics 2000; 25 : 187 - 191.

2. Inhaled endotoxin, a risk for airway disease in some people. Schwartz DA. Respir Physiol 2001 ;128(1):47-55 (PMID: 11535262)

3. Toll-like receptor 4 is involved in the mechanism of early alcohol-induced liver injury in mice. Uesugi T et al. Hepatology 2001 ;34(1):101-8 (PMID: 11431739)

4. Toll-like receptor 4 mediates ozone-induced murine lung hyperpermeability via inducible nitric oxide synthase. Kleeberger SR et al. Am J Physiol Lung Cell Mol Physiol 2001 ;280(2):L326-33 (PMID: 11159012)