Gene name: **HLA-DRA** **Previous HGNC Symbols for HLA-DRA Gene:** HLA-DRA1

External Ids for HLA-DRA Gene: HGNC: 4947 NCBI Gene: 3122 Ensembl: ENSG00000204287 OMIM®: 142860 UniProtKB/Swiss-Prot: P01903

NCBI Gene Summary: HLA-DRA is one of the HLA class II alpha chain paralogues. This class II molecule is a heterodimer consisting of an alpha and a beta chain, both anchored in the membrane. This molecule is expressed on the surface of various antigen presenting cells such as B lymphocytes, dendritic cells, and monocytes/macrophages, and plays a central role in the immune system and response by presenting peptides derived from extracellular proteins, in particular, pathogen-derived peptides to T cells. The alpha chain is approximately 33-35 kDa and its gene contains 5 exons. Exon 1 encodes the leader peptide, exons 2 and 3 encode the two extracellular domains, and exon 4 encodes the transmembrane domain and the cytoplasmic tail. DRA does not have polymorphisms in the peptide binding part and acts as the sole alpha chain for DRB1, DRB3, DRB4 and DRB5.

GeneCards Summary: HLA-DRA (Major Histocompatibility Complex, Class II, DR Alpha) is a Protein Coding gene. Diseases associated with HLA-DRA include Celiac Disease and Graham Little-Piccardi-Lassueur Syndrome. Among its related pathways are TCR Signaling (Qiagen) and Phosphorylation of CD3 and TCR zeta chains. Gene Ontology (GO) annotations related to this gene include *peptide antigen binding* and *MHC class II receptor activity*. An important paralog of this gene is HLA-DPA1.

UniProtKB/Swiss-Prot Summary: An alpha chain of antigen-presenting major histocompatibility complex class II (MHCII) molecule. In complex with the beta chain HLA-DRB, displays antigenic peptides on professional antigen presenting cells (APCs) for recognition by alpha-beta T cell receptor (TCR) on HLA-DR-restricted CD4-positive T cells. This guides antigen-specific T-helper effector functions, both antibody-mediated immune response and macrophage activation, to ultimately eliminate the infectious agents and transformed cells
Cellular localization: lysosome, endosome, extracellular, plasma membrane.

The **HLA-DRA** gene encodes the alpha chain of the **HLA-DR** molecule, a critical component of the major histocompatibility complex (MHC) class II. These molecules are predominantly expressed on antigen-presenting cells, such as monocytes, macrophages, and dendritic cells, and are essential for presenting extracellular antigens to CD4+ T-helper cells, thereby initiating and regulating immune responses.

Function in Sepsis: In sepsis the expression of HLA-DR, particularly on monocytes (mHLA-DR), is notably affected:

Immunosuppression Indicator: A hallmark of sepsis-induced immunosuppression is the downregulation of mHLA-DR expression. Reduced mHLA-DR levels are associated with impaired antigen presentation, leading to decreased T-cell activation and a compromised ability to combat infections.

Diagnostic and Prognostic Role:

- **Biomarker for Immunosuppression:** Quantifying mHLA-DR expression serves as a valuable biomarker for assessing the immune status of septic patients. Low mHLA-DR levels correlate

with increased risks of secondary infections and adverse outcomes, making it a predictive marker for sepsis severity and patient prognosis.
- **Monitoring Recovery:** Dynamic monitoring of mHLA-DR expression can provide insights into the progression or resolution of sepsis-induced immunosuppression, aiding in therapeutic decision-making.

Measurement Techniques:

- **Flow Cytometry:** Traditionally, mHLA-DR expression is measured using flow cytometry, which quantifies the protein levels on the cell surface. However, this method requires specialized equipment and expertise.
- **Quantitative Real-Time PCR (qRT-PCR):** Measuring HLA-DRA mRNA expression via qRT-PCR has emerged as an alternative approach. Studies have demonstrated a strong correlation between HLA-DRA mRNA levels and mHLA-DR protein expression, suggesting that qRT-PCR could serve as a reliable method for evaluating immunosuppression in sepsis.

Therapeutic Implications: Given the association between low mHLA-DR expression and sepsis-induced immunosuppression, therapeutic strategies aimed at restoring mHLA-DR levels are being explored. For instance, granulocyte-macrophage colony-stimulating factor (GM-CSF) has been investigated for its potential to upregulate mHLA-DR expression and enhance immune function in septic patients.