

## Gene Section

### Mini Review

# FCER2 (Fc fragment of IgE, low affinity II, receptor for (CD23))

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## Identity

**Other names:** CD23; CD23A; CLEC4J; FCE2; IGBF

**HGNC (Hugo):** FCER2

**Location:** 19p13.2

## DNA/RNA

### Description

The gene is localized to the short arm of chromosome 19. It contains 11 exons, and spans 13390 bps on minus strand.

### Transcription

Normally expressed in B-cells. Its expression has been shown on T-cells, Langerhans cells, monocytes, macrophages, platelets, and eosinophils as well.

Through alternative splicing 2 major isoforms are produced, FCER2a (CD23a) and FCER2b (CD23b), both of which are expressed on B-cells. FCER2a is constitutively expressed, whereas FCER2b is induced by several cytokines, especially by IL4. There are 3 other splice forms, whose biological significance remains to be determined.

### Pseudogene

N/A

## Protein

### Note

Essential role in the regulation of IgE production as well as differentiation of B cells.

### Description

FCER2 is a Ca<sup>2+</sup>-dependent C-type lectin. The protein

in humans contains 321 amino acids and has a molecular weight of 45 kDa. It has a single membrane-spanning domain. The extracellular domain consists of an alpha-helical coiled coil domain, a lectin head, followed by a short tail region containing an inverse RGD sequence. The coiled coil domain and the lectin head section are critical for the formation of trimers, and IgE binding, respectively. The RGD sequence is a common recognition site of integrins. Through an autocatalytic process involving matrix metalloproteases, the membrane-bound FCER2 is turned into a series of soluble fragments (sFCER2) of molecular weight ranging between 17 and 37 kDa. The soluble forms are also biologically active.

### Expression

FCER2 expression was first described in the thymic medullary B-lymphocytes, and subsequently, in a population of large thymic B-cells with dendritic features which were referred to as asteroid cells. FCER2 is mainly expressed on B cells. It is also expressed on T cells, Langerhans cells, monocytes, macrophages, platelets, and eosinophils. On B cells 2 isoforms are present: a constitutively active form (FCER2a) and an inducible form (FCER2b).

FCER2 expression is upregulated by its own ligand, i.e. IgE. Furthermore, upon treatment with IL4, increased FCER2 expression can be observed in several cell types including eosinophils, neutrophils, macrophages, monocytes, and T cells. In addition, EBV induces CD23 transcription through a regulatory element in intron 1 of FCER2a.

FCER2 expression levels are differentially higher (70%) in mediastinal diffuse large B-cell lymphoma (med-DLBCL) and lower in nonmediastinal nodal DLBCL (15%) and extranodal DLBCL (9%).

## Localisation

Although FCER2 expression is mainly localized to the surface of B-lymphocytes, it is widely distributed on the surface of various other cells including follicular dendritic cells (FDC), and even airway smooth muscle cells.

## Function

FCER2 is the low-affinity immunoglobulin E receptor. It mediates various biological functions. Mainly, it is involved in the down regulation of IgE production by B cells. However, because of its ability to associate with various ligands, its effects on IgE regulation might be stimulatory as well. In fact, FCER2 has been implicated in a variety of cellular functions ranging from cellular adhesion, antigen presentation, growth and differentiation of B and T cells, rescue from apoptosis, release of cytotoxic mediators, and regulation of IgE synthesis.

FCER2 displays susceptibility to proteolytic cleavage which produces a soluble form of FCER2. As the soluble FCER2 does not have the ability to bind to the cell surface, this results in disruption of the feedback inhibition mechanism and increase of IgE production. As a result, soluble FCER2 has mitogenic properties. Furthermore, the proteolytic cleavage of FCER2 is probably the basis of various allergic reactions.

These observations have been supported by cellular and animal models. Antibodies directed against the soluble FCER2 have been shown to inhibit the synthesis of IgE, while cross linking of membrane-bound FCER2 inhibits B-cell growth and differentiation. Furthermore, FCER2-deficient mice produce higher levels of IgE, whereas mice overexpressing membrane-bound FCER2 exhibit weaker IgE responses.

Lumiliximab is an anti-CD23 antibody that is proposed in the therapy of chronic lymphocytic leukemia (CLL). Lumiliximab binds to cell surface membrane FCER, and induce apoptosis. Although previous reports indicated activation of the caspase cascade, the exact mechanism for apoptosis remains to be elucidated.

## Homology

At this time a paralogous gene is not known in humans. It does not show similarity to FCER1, the other member of the immunoglobulin E receptor family.

Orthologues have been shown in mouse, rat and cow, with up to 58% homology at the protein level. However, some of the domains required for the proper function of human FCER2 is absent in orthologues. For example, the murine FCER2 does not have the RGD motif nor does it retain the IgE-binding affinity.

## Mutations

### Germinal

An arginine to tryptophane substitution of amino acid 62 (p.R62W) have been suggested to affect the receptor function and the mitogenic role of the protein. This

suggestion was based on in vitro studies which showed the mutant protein was resistant to proteolytic cleavage following treatment with a broad range of proteases.

### Somatic

N/A

## Implicated in

### Mediastinal diffuse large B-cell lymphoma (Med-DLBCL)

#### Disease

Med-DLBCL is a subtype of DLBCL that arise in the mediastinum from putative thymic B-cell origin. Its clinical, immunophenotypic, and genotypic features are distinctive. However, it has significant morphologic and immunophenotypic similarities with classical Hodgkin lymphoma (CHL) involving mediastinum. Since the prognosis and the first line of therapy for these conditions differ significantly, previous studies highlighted the usefulness of CD23 expression in the differential diagnosis of these conditions. Up to 85% of med-DLBCL patients are positive for FCER2, whereas only 10% of CHL patients show a weak FCER2 staining, suggesting that FCER2 might be helpful to distinguish between med-DLBCL and CHL.

#### Cytogenetics

N/A

### Chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL)

#### Disease

CD23 positivity is noted in most cases of CLL/SLL and is used to differentiate CLL/SLL from mantle cell lymphoma that shares the CD5+ B-cell phenotype. The lack of CD23 in mantle cell lymphoma along with the dim expression of CD20 and light chain in CLL often help in this important distinction given the difference in prognosis and therapeutic options. However, some case of CLL/SLL may have an atypical phenotype including the lack of CD23 expression; posing diagnostic difficulty.

#### Cytogenetics

N/A

### Nodal marginal zone B-cell lymphoma (NMZL)

#### Disease

NMZL is a rare form of non-Hodgkin lymphoma with primary presentation in the lymph node in the absence of clinical evidence of prior or concurrent involvement of extranodal sites or spleen. In a comprehensive study, FCER2 was found to highlight neoplastic cells in a case in which the staining was diffuse but weakly positive. Furthermore, the FCER2 staining highlighted residual and disrupted follicular dendritic cell (FDC) meshwork in 40% of the NMZL cases that were also highlighted by CD21 staining.

**Cytogenetics**

N/A

**Follicular lymphoma (FL)****Disease**

CD23 positivity by immunohistochemical analysis has been recently linked to a specific anatomic site in FL. Thorns et al. (2007) found that FLs in inguinal lymph nodes were more commonly CD23+ compared with FL from other anatomic sites. Katzenberger et al. (2009) demonstrated a high proportion of CD23+ cases in FLs with a diffuse growth pattern and a specific chromosomal alteration (deletion 1p36). CD23 expression in FL was most recently reported to be associated with favorable outcome by Olteano et al. (2011) who also reported that CD23 positivity was more common in inguinal lymph nodes and in low-grade cases. They postulated that CD23 expression is at least partially modulated by the tissue- and/or host-specific factors (such as anatomic site or lower histologic grade) and suggested CD23 expression may be a surrogate for a certain host-specific (possibly, immune) environment that is associated with a more indolent disease course and, thus, with a favorable outcome.

**Cytogenetics**

N/A

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