

## Gene Section

### Mini Review

# MAML2 (mastermind-like 2)

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## Identity

**Hugo:** MAML2

**Other names:** hMam-3; KIAA1819

**Location:** 11q21

## DNA/RNA

### Description

Spans 365 kb; 5 exons.

### Transcription

A major transcript of 7.5 kb.

## Protein

### Description

1153 aa, 125 kDa; conserved N-terminal basic domain (aa 29-92) which binds to the ankyrin repeat domain of Notch receptors; two acidic domains (aa 263-360 and 1124-1153) and a C-terminal transcriptional activation domain.

### Expression

Widely expressed.

### Localisation

Nuclear granules.

### Function

Mastermind-like coactivator for all four Notch receptors; forms a complex with the Notch intracellular domain (Notch ICD) and the CSL family of transcription factors (CSL: CBF1/RBP-jk, Suppressor of Hairless, LAG1), resulting in activation of the Notch

target genes HES1 and HES5; functions as a CSL-dependent transcriptional coactivator for ligand-stimulated Notch.

### Homology

MAML1 and MAML3.

## Implicated in

### *Mucoepidermoid carcinoma with t(11;19)(q21-22;p13)*

#### Disease

- Most common type of malignant salivary gland tumor;
- Second most frequent lung tumor of bronchial gland origin;
- Rare tumour in the thyroid.

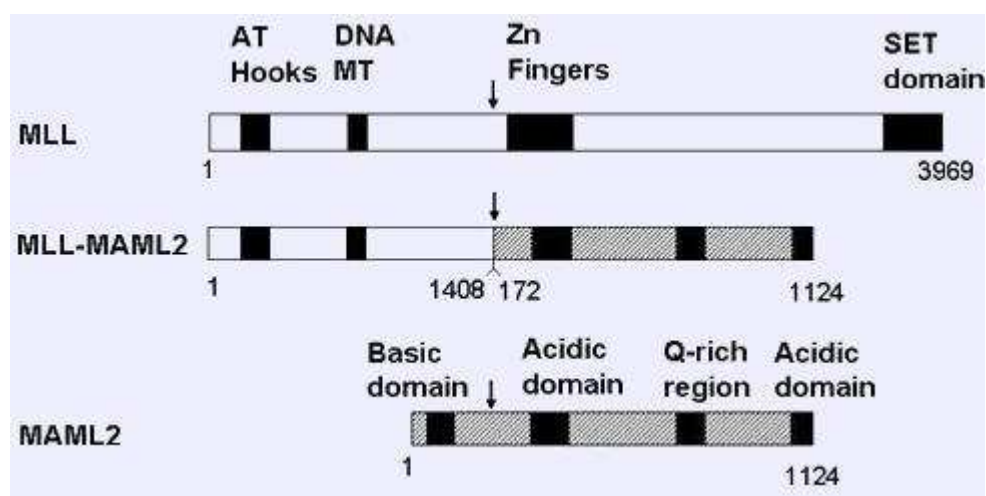
The t(11;19) was found in samples from the three different sites.

#### Prognosis

- Mucoepidermoid carcinomas have an unpredictable behaviour.
- The CRTC1-MAML2 fusion transcript was found equally in low, intermediate and high grade tumours; however, tumours lacking the fusion transcript were significantly associated with metastases; they may represent a subset of aggressive tumours.
- In another study, the median survival for fusion-positive patients was greater than 10 years compared to 1.6 years for fusion-negative patients.

#### Hybrid/Mutated Gene

CRTC1-MAML2; exon 1 of CRTC1 fused to exons 2-5 of MAML2. Note: CRTC1 is also known as MECT1, or WAMTP1.



### Abnormal Protein

**CRTC1-MAML2.** In the fusion protein, the first 171 aa including the basic domain of MAML2 are replaced by 42 aa of CRTC1; there are no sequence similarities in the N-terminal domains of MAML2 and CRTC1. The fusion protein activates transcription of the Notch target gene HES1 independently of both Notch ligand and CSL.

Transforming activity of CRTC1-MAML2 fusion oncoprotein is mediated by mimicking constitutive activation of cAMP signaling, by activating CREB directly.

### Warthin's tumor with *t(11;19)(q21-22;p13)*

**Note:** In rare instances mucoepidermoid carcinoma may arise from or coexist with Warthin's tumors.

### Disease

Warthin's tumor is a salivary gland neoplasm consisting of benign epithelial and lymphoid components; malignant transformation is extremely rare.

### Hybrid/Mutated Gene

CRTC1-MAML2

### Clear cell hidradenomas of the skin with *t(11;19)(q21-22;p13)*

### Disease

Clear cell hidradenomas of the skin are benign sweat gland tumors of eccrine duct origin.

### Hybrid/Mutated Gene

CRTC1-MAML2; exon 1 of CRTC1 fused to exons 2 of MAML2.

### *inv(11)(q21q23)* in therapy related leukemias

### Disease

Therapy-related acute leukemia and MDS.

### Hybrid/Mutated Gene

MLL-MAML2; exon 1-7 of MLL fused to exons 2-5 of MAML2.

### Abnormal Protein

Hybrid transcript MLL/MAML2 contains the following domains: from MLL: AT-hook, DNA-Methyltransferase; from MAML2: Q rich domain, acidic domain.

## To be noted

**Note:** It is amazing that a similar fusion transcript (CRTC1-MAML2) can be seen both in a benign and in a malignant tumour of the same organ: Warthin's tumor, a benign salivary gland neoplasm, and mucoepidermoid carcinoma of the salivary gland: either another event differentiate the two, or the genetic event takes place in different cell types or in a given cell type at different states of differentiation.

It has been hypothesized that CRTC1-MAML2 fusion is etiologically linked to benign and low-grade malignant tumors originating from diverse exocrine glands rather than being linked to a separate tumor entity.

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