

## Gene Section

### Review

# NACC1 (nucleus accumbens associated 1, BEN and BTB (POZ) domain containing)

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### Identity

**Other names:** BEND8, BTBD14B, NAC-1, NAC1

**HGNC (Hugo):** NACC1

**Location:** 19p13.2

**Local order:** Gene orientation: telomere-3' NACC1 5'-centromere.

### DNA/RNA

#### Description

The NACC1 gene is encoded by 5 exons spanning 5958 base pairs that are located on chromosome 19p13.13.

#### Transcription

4556 bp linear mRNA. The coding sequence (1584 bp) is from 169-1752 bp.

### Protein

#### Description

NACC1 consists of 527 amino acids and the protein is predicted to have a molecular weight of 57258 Da (Stead et al., 2009). Comprising of a N terminal BTB/POZ domain and the C terminal BEN domain, NACC1 is missing a Zinc Finger domain unlike many members of the BTB/POZ family. The homodimerization of NACC1 mediated by the BTB domain is thought to be essential for its functional activities (Nakayama et al., 2006). The newly defined

BEN domain may mediate protein-DNA interactions (Abhiman et al., 2008), however it remains to be investigated if NACC1 is indeed a DNA binding protein.

#### Expression

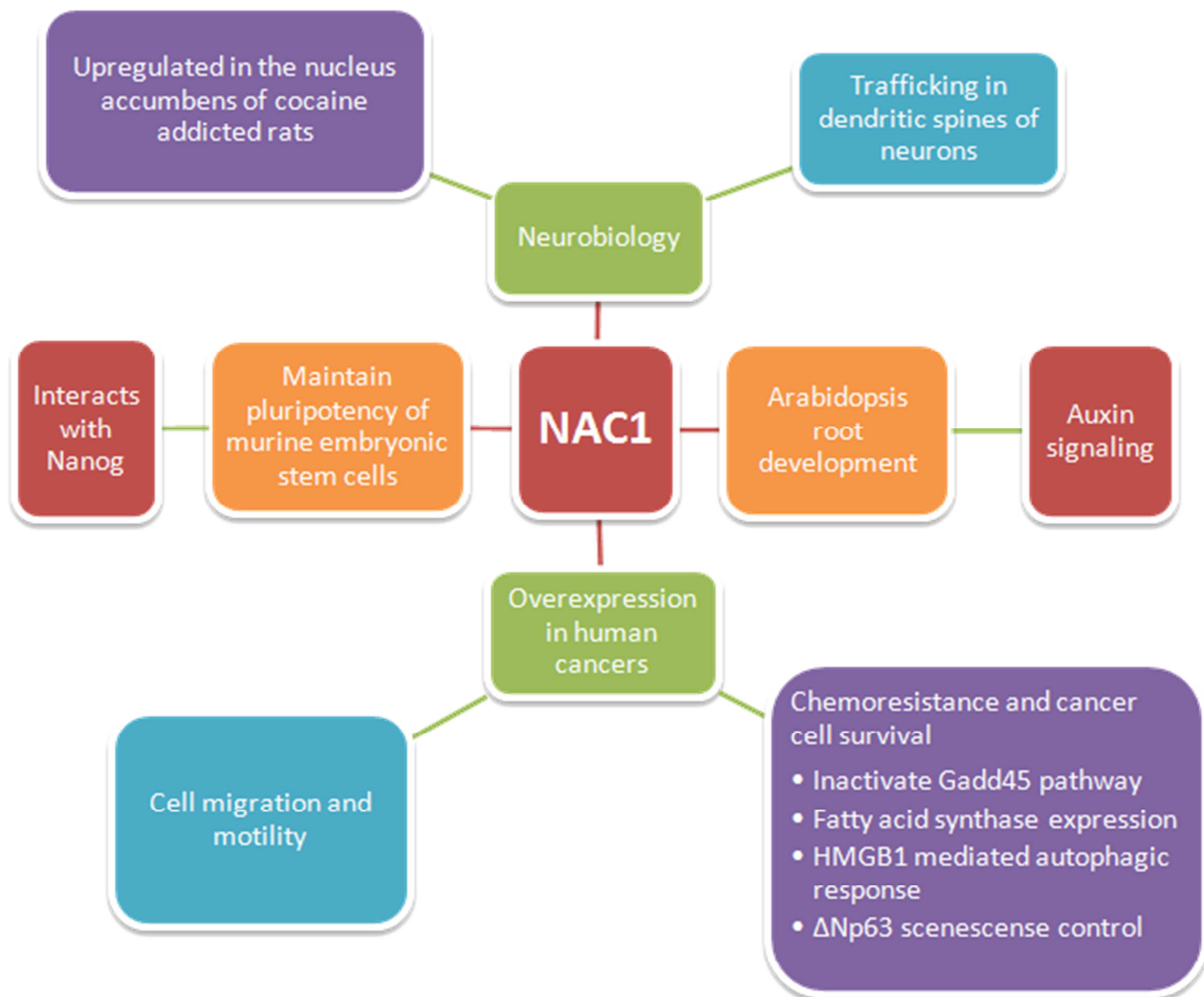
Expressed in Arabidopsis root as a transcription activator, found in nuclear accumbens of neuronal tissues and overexpressed in various human neoplastic diseases (Cha et al., 1997; Xie et al., 2002; Guo et al., 2005; Nakayama et al., 2006; Shen et al., 2007; Nakayama et al., 2007; Yeasmin et al., 2008; Mackler et al., 2008; Ishibashi et al., 2009; Korutla et al., 2009; Ishikawa et al., 2010; Yeasmin et al., 2011).

#### Localisation

Nucleus and cytoplasm. Dynamic changes in subcellular localization of NACC1 at the different phases of cell cycle progression were documented. In non-mitotic cells, NACC1 accumulated in distinct nuclear punctate bodies. During mitosis, these punctate nuclear bodies dissolve into a diffuse pattern of distribution in the cytoplasm. NACC1 nuclear bodies reappeared once mitosis was completed and the nuclear membrane reformed. (Wu et al., 2011).

#### Function

First identified as a novel transcript in the nucleus-accumbens of cocaine-addicted rats (Cha et al., 1997), NACC1 was known as a transcriptional corepressor (Korutla et al., 2009) with well defined functions in the murine neurologic physiological pathways (Shen et al., 2007; Mackler et al., 2008) and Arabidopsis root development (Xie et al., 2002; Guo et al., 2005).



**Functions of NAC1 in various systems and pathways.**

The role of NAC1 in human cancer was unknown. Preliminary studies of SAGE (Serial Analysis of Gene Expression) libraries were conducted to elucidate the role of NAC1 in the pathogenesis of human cancers and had revealed the higher expression levels of NAC1 in tumor samples as compared to the normal tissues in various cancer types such as pancreas, liver, and breast (Nakayama et al., 2006). Following that, detailed gene expression studies were undertaken in patient tumor samples and characterized the overexpression of NAC1 in cervical carcinoma and ovarian high-grade serous carcinoma, one of the most lethal neoplastic diseases in women (Nakayama et al., 2006; Nakayama et al., 2007; Yeasmin et al., 2008; Ishibashi et al., 2009; Jinawath et al., 2009; Nakayama et al., 2010; Ishikawa et al., 2010; Shih et al., 2011; Yeasmin et al., 2011). Amplification of NACC1 has also been recently reported in ovarian cancer, and analysis of The Cancer Genome Atlas data set revealed that NACC1 was one of the top potential "driver" genes that showed the highest correlation

between DNA and RNA copy number in ovarian high-grade serous carcinomas (Shih et al., 2011). Additionally, NAC1 up-regulation is associated with disease aggressiveness and contributes to the development of chemo-resistance (Nakayama et al., 2006; Jinawath et al., 2009; Nakayama et al., 2010; Zhang et al., 2012). NAC1 enables the survival and growth of ovarian cancer cells by regulating several downstream targets including those involved in Gadd45 cell survival pathway (Nakayama et al., 2007; Jinawath et al., 2009), fatty acid metabolism (Ueda et al., 2010), and HMGB-1 mediated autophagic response (Zhang et al., 2012). NAC1 function has also been demonstrated to be essential for the migration of ovarian and melanoma cancer cells (Yamazaki et al., 2005; Nakayama et al., 2010). Mouse tumor xenograft studies illustrated the *in vivo* therapeutic potential of inactivating Nac1 function; as such manipulation in SKOV3 ovarian cancer cells and HeLa cervical cancer cells was demonstrated to be sufficient to inhibit the

growth of tumor xenografts (Nakayama et al., 2006). Nac1 is more recently associated with maintenance of the pluripotency of mouse embryonic stem cells through its interaction with Nanog (Wang et al., 2006; Ma et al., 2009).

### Homology

BEN1 domain, BTB/POZ domain.

## Implicated in

### Ovarian serous carcinoma

#### Disease

NACC1 is highly overexpressed in ovarian carcinomas. High NAC1 expression is correlated with early tumor recurrence (Nakayama et al., 2006). Nakayama et al. found there is significant correlation between poor prognosis and the expression of NAC1 in patients who received taxol therapy. In addition, high immunoreactivity to NAC1 in the primary ovarian tumor is able to predict early tumor recurrence. The mechanism of over expression of NAC1 in ovarian serous carcinoma is by amplification of the gene locus ch19p13.2 carrying the NACC1 gene (Shih et al., 2011). NAC1 function is important for the survival and proliferation of ovarian cancer cells, and increases their migration and motility (Nakayama et al., 2010). Zhang et al. found that NAC1 is also implicated in autophagic response in the ovarian cancer cell line, which may contribute to the development of chemoresistance (Zhang et al., 2012).

### Cervical carcinomas

#### Disease

Using immunohistochemistry, Yeasmin et al. found that NACC1 is more frequently overexpressed in cervical adenocarcinomas and adenosquamous carcinomas as compared to squamous cell carcinomas (Yeasmin et al., 2008). In squamous cell carcinomas that have overexpression of NAC1, NACC1 gene amplification was detected, and positive NAC1 expression is linked to shorter overall survival. NAC1-silenced cancer cells undergo growth inhibition, increased apoptosis, decreased proliferation, cellular migration and invasion.

### Endometrial carcinomas

#### Disease

NAC1 was found to be overexpressed in the normal endometrium in the early and mid proliferative phases by the actions of circulating estrogen (Ishibashi et al., 2009). Ishikawa et al. found that there were significant correlations between positive NAC1 expression and pathological grade in endometrial carcinomas (Ishikawa et al., 2010). Endometrial carcinomas with NAC1 overexpression were found to be clinically aggressive, high-grade carcinomas. However unexpectedly they also found that during the

progression from normal endometrium to hyperplasia and finally to carcinoma, there is a stepwise reduction in NAC1 protein expression. It was proposed that this might be related to loss of estrogen signaling in development of endometrial cancers (Ishibashi et al., 2009).

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