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# Gene Section
## Short Communication

# ATG2B (Autophagy-related 2B)

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## Abstract

Autophagy is a cellular process involved in the sequestration of cytosolic components and their degradation by lysosomes. Autophagy has been involved in physiological responses to stress or aging and in the development of many human diseases including solid and haematological cancers. In humans, 16 autophagy-related genes are known. The ATG2B protein is involved in the late steps of the autophagy process i.e. the formation of autophagosomes that fuse with lysosomes before degradation. Loss-of -function (frameshift) acquired mutations of ATG2B have been identified in gastric and colorectal carcinomas with high microsatellite instability. Both pharmacologic and genetic evidence indicate that autophagy plays pleiotropic functions in hematopoietic cell homeostasis and leukemogeneis. Autophagy could exert two opposite roles (cell death and survival) depending on the nature of the hematopoietic malignancy.

The germline duplication of ATG2B and GSKIP, both located in 14q32.2, predisposes to the development of familial myeloproliferative neoplasms with autosomal dominant inheritance, in particular essential thrombocythemia progressing to leukemia. Overexpression of ATG2B and GSKIP enhances megakaryocyte progenitor differentiation by increasing progenitor sensitivity to thrombopoietin. Both genes cooperate with somatic JAK2, MPL and CALR mutations and their overexpression provides a growth advantage to hematopoietic cells carrying these driver mutations that may explain the familial aggregation and the progression of essential thrombocythemia to myelofibrosis and leukemia.

**Keywords**

ATG2B; Myeloproliferative neoplasms (MPN); essential thrombocythemia; myelofibrosis; leukemia; predisposition; ATG2B/GSKIP; chromosome 14; CNV; autophagy; Wnt/beta-catenin pathway

## Identity

**Other names:** C14orf103

**HGNC (Hugo):** ATG2B

**Location :** 14q32.2

**Location (base pair)**

ATG2B starts at 96.745.539 and ends at 96.829.738 bp (on Assembly GRCh37)

**Local order**

telomere to centromere.

**Note**

cooperates with GSKIP, also located in 14q32.2 and included in the 700 kb duplication NC_000014.9:g.96.163.103_96.857.129dup (on Assembly GRCh37)

## DNA/RNA

### *Description*

The ATG2B gene consists of 42 exons spanning a region of 82.08 kb.

### Transcription

A single mRNA transcript (NM_018036.6) of the ATG2B gene, with a total length of 6234 nucleotides, has been annotated.

### Pseudogene

Not yet identified.

## Protein

### Description

The protein encoded by the ATG2B gene is the autophagy-related protein 2 homolog B of 2078 amino acids, with a calculated molecular mass of 232.8 kDa

### Expression

Expression of ATG2B has been detected in various normal human tissues (bone marrow, whole blood, thymus, brain, heart, muscle, colon, kidney, liver, lung, pancreas, thyroid, salivary and adrenal glands, skin, ovary, uterus, placenta, prostate and testis).
In hematopoietic cells, ATG2B is expressed in $CD34^+$ purified hematopoietic progenitors and $CD36^+$ erythroblasts or $CD41^+$ megakaryocytes derived from $CD34^+$ progenitors cultured in vitro (Saliba et al, 2016)

### Localisation

ATG2B is mainly localized in the nucleus.

### Function

Autophagy is an intracellular degradation system by which cytoplasmic materials are enclosed by the autophagosomes and transferred to lysosomes before degradation. The autophagy process has been extensively studied in yeast; 35 autophagy-related genes (ATG) have been identified, of which 16 are currently known in humans . This cellular process is a highly conserved among species. In humans, two ATG2 proteins, ATG2A and ATG2B, have redundant functions and are required for autophagosome formation (Velikkakath AK et al , 2012).

### Homology

44.5% of human ATG2B residues are identical to those of human ATG2A.

## Mutations

### Germinal

A germline 14q32.2 head-to-tail duplication of 700 kb has been associated with familial myeloid malignancies (Saliba et al , 2015). The germline duplication includes the genes TCL1A, GSKIP, ATG2B, BDKRB1, BDKRB2 and the first exon of AK7. The overexpression of ATG2B and GSKIP that are expressed in myeloid cells, enhances hematopoietic progenitor differentiation, particularly of megacaryocytes. The development of myeloid malignancies required the cooperation of both genes with the myeloproliferative neoplasms (MPN) driver JAK2 $^{Val617Phe}$ mutation, MPL or CALR mutations. The mechanism of cooperation between ATG2B and GSKIP with MPN driver mutations remains unknown.
The germline duplication with the same distal and proximal breakpoints has only been identified in MPN families originated from West Indies (Martinique) suggesting a founder effect.

### Somatic

A loss-of-function somatic mutation (c.3120delA, p.Lys1040fs) in gastric carcinomas (15.6%) and in colorectal carcinomas (11.6%) (Klionsky DJ, 2009).

## Implicated in

### Familial myeloproliferative neoplasms (MPN)

**Disease**

Familial MPN, in particular, essential thrombocythemia progressing to myelofibrosis and/or acute myeloid leukemia and primary myelofibrosis, with autosomal dominant inheritance and originated from West-indies (Martinique) may be linked to ATG2B/GSKIP germline duplication. The predisposition is highly penetrant (80%) and is characterized by an earlier age of MPN onset in comparison to sporadic cases (41 years versus > 60 years). The spectrum of acquired driver mutations (JAK2 $^{Val617Phe}$, MPL and CALR mutations) is similar to the spectrum of mutations in sporadic MPN cases.

**Prognosis**

The percentage of transformation is close to 50% in these familial MPN cases and is related to the detection of mutations affecting epigenetic regulator genes such as TET2 IDH1 or IDH2.

### Acute myeloid leukemia (AML)

**Disease**

AML originated from West-indies (Martinique) may be linked to ATG2B/GSKIP germline duplication.

**Prognosis**

The prognosis of the disease is also linked to the detection of acquired mutations in TET2, IDH1 or in IDH2.
No TP53 mutation was found, contrary to what was observed in AML evolving from MPN, suggesting a different pathway for leukemic transformation.

### Gastric carcinoma

Loss-of-functions somatic mutations in ATG genes (ATG2B, ATG5, ATG9B and ATG12) are identified

in 28% of gastric carcinomas with high microsatellite instability. These mutations may contribute to cancer development by deregulating the autophagy process (Kang et al, 2009).

### *Colorectal cancer*

Loss-of-functions somatic mutations in ATG genes (ATG2B, ATG5, ATG9B and ATG12) are identified in 28% of colorectal carcinomas with high microsatellite instability. These mutations may contribute to cancer development by deregulating the autophagy process (Kang et al, 2009).

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